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TREATMENT OF CARDIOVASCULAR SYPHILIS

RESULTS OBTAINED IN FIFTY-THREE PATIENTS WITH AORTIC ANEURYSM AND IN ONE HUNDRED AND TWELVE WITH AORTIC REGURGITATION

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In 1930, two of us (J. E. M. and J. H. D.) presented before the American Heart Association a preliminary report [1] dealing with the major question of the prolongation of life as a result of treatment in 43 patients with aortic aneurysm, 90 with aortic insufficiency and 8 with various other forms of syphilitic heart disease. Because of limitations of space, it was not possible to discuss other than the one major issue, and consideration of other data was deferred. Meanwhile we have kept in touch with the patients originally reported on and have added others. In this paper, we offer a general consideration of the treatment of cardiovascular syphilis, based now on 53 patients with aortic aneurysm and 112 with aortic regurgitation. The 8 patients with syphilitic myocarditis, aortitis or angina pectoris included in the original paper have been left out of consideration, since the discussion at the meeting brought out some skepticism as to the validity of these diagnoses. We have therefore purposely limited our study to cases of aortic aneurysm and aortic regurgitation, since in these two groups of cases there can be little or no question of the accuracy of clinical diagnosis.

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From the Syphilis Division of the Johns Hopkins Hospital.

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1. Moore, J. E., and Danglade, J. H.: The Treatment of Cardiovascular Syphilis: A Study of the Duration of Life in 141 Treated and Untreated Patients with Aortic Regurgitation and Aortic Aneurysm, Am. Heart J. **6**:148, 1930.

We realize, and have emphasized elsewhere,[2] that the arrest, improvement or amelioration of symptoms of cardiovascular syphilis is *a priori* more likely if treatment is started in the stage of simple uncomplicated aortitis than if it is deferred until the advent of extensive anatomic damage to the aortic wall or valve cusps. Since there is doubt in the minds of many competent internists[3] that the diagnosis of uncomplicated aortitis can be made with assurance in the absence of aneurysm or of valvular insufficiency, we have preferred to defer consideration of the results of treatment in aortitis until we had completed a study of the accuracy of diagnosis in this condition.[2] The prevailing pessimism as to the beneficial effect of treatment in cardiovascular syphilis was an added reason which prompted us to review first our cases of aneurysm and aortic regurgitation. If we can show that the patients with these graver lesions can be benefited by treatment, it will be less difficult to convince others of the validity of our conclusions in uncomplicated aortitis, subsequently to appear. We realize also the limitations of treatment in cardiovascular syphilis, that the mechanical circulatory defect cannot be remedied, and that the most one can expect is arrest of progress in the inflammatory process, amelioration of symptoms and prolongation of life. It is from this point of view that we approach our material.

PROPHYLAXIS OF CARDIOVASCULAR SYPHILIS

Obviously, if early syphilis could be adequately treated in every instance, the incidence of cardiovascular syphilis would be much reduced. As has been so often said of neurosyphilis, especially tabes dorsalis and dementia paralytica, so also it may be aptly said of cardiovascular syphilis: The best way to treat it is to prevent it. Several years ago, one of us (J. E. M.) with J. E. Kemp published[4] the details of the clinical outcome in 402 patients with early syphilis. These patients had been followed for from one to nine years after varying amounts of treatment. From time to time during the period of observation, each of them was carefully reexamined, often repeatedly, with especial emphasis on examination of the nervous system and of the cardiovascular apparatus. For purposes of study, they were divided into four treatment groups as follows:

Group 1. Patients receiving from one to eight injections of an arsphenamine product, mercury being used not at all for less than one month.

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2. Moore, J. E.; Danglade, J. H., and Reisinger, J. C.: The Diagnosis of Syphilitic Aortitis Uncomplicated by Aortic Regurgitation or Aneurysm: A Comparison of Clinical and Necropsy Findings in One Hundred and Five Patients, Arch. Int. Med. **49**:753 (May) 1932.

3. Conner, L. A., in discussion of paper by Steel, D.: Am. Heart J. **6**:65, 1930.

4. Moore, J. E., and Kemp, J. E.: The Treatment of Early Syphilis: II. Clinical Results in 402 Patients, Bull. Johns Hopkins Hosp. **39**:16, 1926.

Group 2. Patients receiving from one to two courses of arsphenamine (from six to twelve injections), mercury having been used for at least two months during the interim between courses of arsphenamine.

Group 3. Patients receiving three courses of arsphenamine (from thirteen to twenty injections) and treatment with mercury during the interim.

Group 4. Patients receiving four or more courses of arsphenamine (from twenty-one to forty injections) and treatment with mercury during the interims.

The results of prolonged observation, so far as cardiovascular syphilis is concerned, are summed up in table 1. These data, gathered during the study with Kemp, were unpublished at the time. In 24 patients who were inadequately treated according to modern standards, cardiovascular syphilis was observed to develop. The final diagnoses were: uncomplicated syphilitic aortitis in 21, aortic regurgitation in 2 and aortic aneurysm in 1. This type of lesion developed in 9.6 per cent of the patients in group 1, and in 5.6 per cent of those in group 2. In not a single patient among the 117 who had received three or more

TABLE 1.—*Prophylaxis of Cardiovascular Syphilis by Adequate Treatment for Early Syphilis*

Treatment Group	Number of Patients with Early Syphilis in Group	Number in Whom Cardiovascular Syphilis Subsequently Developed	Percentage in Whom Cardiovascular Syphilis Developed
Group 1	196	19	9.6
Group 2	89	5	5.6
Group 3	46	0	0
Group 4	71	0	0

courses of arsphenamine and treatment with a heavy metal preparation during the interims did any evidence of cardiovascular syphilis develop during the period of observation. It was recognized that the actual incidence of cardiovascular syphilis was probably higher than we had indicated, and that in subsequent years more patients, both from the adequately and from the inadequately treated groups, would probably show this late complication. This is to be expected, since, as is already well known, and as we shall emphasize presently, the average interval of time between infection and the appearance of cardiovascular syphilis is about twenty years, while in the group of patients with early syphilis studied the maximum posttreatment period of observation did not exceed nine years. In the cases actually observed, however, the average interval between the last treatment and the detection of the cardiovascular lesion was only forty-six months, indicating that inadequate early treatment may hasten the onset of cardiac complications.

We believe that, even if the relatively short duration of observation is considered, these data are convincing evidence of the protective effect of reasonably adequate treatment for early syphilis, and that they indi-

cate that cardiovascular syphilis might be largely eliminated if it were possible to treat adequately every patient with primary or secondary syphilis. This problem will be approached from a somewhat different angle when we come to consider the question of the treatment for early syphilis received by the 165 patients with cardiovascular syphilis in this study.

INCIDENCE OF SYPHILIS OF HEART AND AORTA

Several years ago a committee of the American Heart Association, composed of Drs. Pardee, Carter, Eggleston, Krumbhaar, Marvin, White and Wilson, suggested an outline for the study of cardiovascular syphilis, including six major topics. These were: incidence, pathology, symptoms, physical signs, criteria for diagnosis and treatment. The material at our disposal permits us to consider in some detail the questions of incidence and treatment. The pathology of cardiovascular syphilis has been studied in this country especially by the Cleveland [5] and Ann Arbor groups.[6] The symptoms, physical signs and criteria of diagnosis have been reviewed exhaustively by many observers, prominent among whom is Reid.[7] These are again being critically examined by Carter and Baker of this university, who have published a preliminary paper [8] and whose detailed studies are expected to appear in monographic form. In this paper, we purposely omit an analysis of symptoms, physical signs, roentgenologic diagnoses and electrocardiographic changes. Data on these features would obscure our main argument concerning treatment. In the patients included in this series, the diagnosis of aneurysm or of aortic regurgitation was obvious. It is important, however, to consider questions of incidence in some detail, since they help in defining our material. Furthermore, since the population of Baltimore includes a large number of Negroes, we have an exceptional opportunity not only to observe large numbers of patients with cardiovascular syphilis, but also to compare the behavior of the disease in the white and colored races.

Questions as to the incidence of cardiovascular syphilis may be approached in a variety of ways. Actuarial estimates indicate that 2 per cent of the population of the United States are suffering from

5. Saphir, O., and Scott, R. W.: Observations on 107 Cases of Aortic Insufficiency with Special Reference to the Aortic Valve Area, the Myocardium, and Branches of the Aorta, Am. Heart J. **6**:56, 1930.

6. Warthin, A. S.: The Distribution of Latent Syphilis in the Population, De Lamar Lectures, Johns Hopkins School of Hygiene and Public Health, Baltimore, Williams & Wilkins Company, 1930.

7. Reid, W. D.: The Diagnosis of Cardiovascular Syphilis: Analysis of Clinical and Post-Mortem Findings, Am. Heart J. **6**:91, 1930.

8. Carter, E. P., and Baker, B. M., Jr.: Certain Aspects of Syphilitic Cardiac Disease, Bull. Johns Hopkins Hosp. **48**:315, 1931.

organic heart disease.[9] White [10] presented a table compiled from various sources, which points out that in different parts of the world, and in various social classes, from 5 to 25 per cent of all cases of organic heart disease are due to syphilis. Perhaps a satisfactory median would be from 10 to 15 per cent. If these estimates are correct, and if the lowest estimate (10 per cent) for the ratio of syphilitic to organic heart disease is used, there are at least 240,000 patients in this country with syphilitic heart disease.

The clinical incidence of cardiovascular syphilis among syphilitic patients in our own clinic is shown in table 2. These data are taken from Turner's paper,[11] and are based on the admission diagnoses of 10,000 consecutive patients with syphilis. In estimating percentages, however, only the 6,420 patients with late syphilis are used, since in the early stages of the disease detectable lesions of the heart and aorta are

TABLE 2.—*Percentage Incidence of Cardiovascular Syphilis by Race and Sex Among 6,420 Patients with Late Syphilis (After Turner)*

Cardiovascular Condition	Percentage Incidence				
		White Patients		Colored Patients	
	Total	Male	Female	Male	Female
Aneurysm of aorta	1.2	1.2	0.3	3.0	0.7
Aortic regurgitation	2.7	2.8	1.4	5.0	1.5
Other forms of cardiovascular syphilis	6.2	4.7	3.1	9.9	5.0
Total incidence*	10.1	7.2		11.4	

* The percentage of incidence of cardiovascular syphilis in the total number of males was 13.9; in the total number of females, 6.7.

so rare as to be negligible. The rates of incidence for aneurysm of the aorta and aortic regurgitation, which form the subject matter of this paper, are given separately. The caption "other forms of cardiovascular syphilis" includes uncomplicated syphilitic aortitis, angina pectoris, myocarditis, etc. Aortitis is, of course, the most frequent of these. As Turner pointed out, cardiovascular syphilis is more frequent in males than in females in the proportion of two to one, and more frequent in Negroes than in whites. The Negro male is almost four times as liable to acquire this lesion as the white female. That there is a definite race and sex predilection there can be no doubt. The excessively high rate among colored males is usually attributed to the influence of hard physical labor. That this can hardly be the only explanation is indicated

9. Dublin, L. I.: Statistical Aspects of the Problem of Organic Heart Disease, Am. Heart J. **1**:359, 1926.

10. White, P. D.: Heart Disease, New York, The Macmillan Company, 1931, pp. 302-303.

11. Turner, T. B.: The Race and Sex Distribution of the Lesions of Syphilis in 10,000 Cases, Bull. Johns Hopkins Hosp. **46**:159, 1930.

by the fact that the percentage incidence in colored females (7.2) is almost equal to that in white males (8.7).

It is a curious and as yet unexplained statement that cardiovascular syphilis appears to be as uncommon in the African Negro resident in the tropics as it is common in the American Negro (Manteufel,[12] McArthur[13]). Like the lower incidence of neurosyphilis in the tropics, this is usually attributed to the lazy, care-free life of the African Negro, in contrast to the strain of civilization and the hard physical labor to which his American brother is subjected. To the skeptic, a much more logical explanation would appear to lie in the almost inextricable confusion of syphilis and frambesia in the tropics, on the one hand, and, on the other, to inadequate clinical study. The evidence so far adduced as to the actual absence of cardiovascular lesions in tropical syphilis is unconvincing.

TABLE 3.—*Race and Sex Incidence of Aneurysm and Aortic Regurgitation in This Series of Patients*

Cardiovascular Condition	Total Number of Cases	Number of Cases in					
		White Males	White Females	Total White Group	Colored Males	Colored Females	Total Colored Group
Aneurysm	53*	12	..	12	33	8	41
Aortic regurgitation	112	29	10	39	57	16	73
Totals†	165	41	10	51	90	24	114

* In nine, aneurysm was complicated by aortic regurgitation.
† Total for males, 131; total for females, 34.

The race and sex distribution of the 165 cases of this study is shown in table 3. Drawn from the larger material of table 2, the figures in table 3 of course parallel those in table 2 closely. Nine patients with both aneurysm and aortic insufficiency have been classified with the aneurysm group, and this classification is retained throughout the paper.

From the pathologic standpoint, the incidence of cardiovascular syphilis, especially of syphilitic aortitis, is vastly higher than the acumen of clinical diagnosis would indicate. Careful studies of syphilitic patients at necropsy show that aortitis is present in from 70 (Langer[14]) to 90 per cent (Warthin[15]). In the majority of these, the lesion must be below the level of clinical recognition. In only 39.3 per cent of Langer's patients (including those with simple aortitis, those with aortic regurgi-

12. Manteufel, P.: Syphilis in den Tropen, in Jadassohn: Handbuch der Haut- und Geschlechts-Krankheiten, Berlin, Julius Springer, 1928, vol. 17, pt. 3.

13. McArthur, D. C.: Syphilis in the Bechuanaland Native: Some Points Wherein It Differs from That Seen in the European, Brit. J. Dermat. **35**:411, 1923.

14. Langer, E.: Die Häufigkeit der luetischen Organveränderungen insbesondere der Aortitis luetica, München. med. Wchnschr. **73**:1782, 1926.

15. Warthin, A. S.: The Lesions of Latent Syphilis, South. M. J. **24**:273, 1931.

tation and those with aneurysm) was the condition correctly diagnosed during life. We recently showed [2] that the diagnosis of uncomplicated aortitis (excluding aortic regurgitation and aneurysm) was correctly made or suspected ante mortem in only 16.2 per cent of 105 patients in whom the lesion was found at necropsy.

Obviously, therefore, every patient with inadequately treated late syphilis must be suspected of having syphilitic aortitis, and in at least

TABLE 4.—*Age of Patients with Aneurysm and Aortic Regurgitation in This Series, on Admission to Hospital*

	Total Number of Patients	Number Who on Admission Were of Age Given				
		21-30 Yr.	31-40 Yr.	41-50 Yr.	51-60 Yr.	61-70+ Yr.
Patients with aneurysm						
White						
Males	12	..	2	2	4	4
Females	..	..	..	..	..	..
Colored						
Males	23	3	12	11	7	..
Females	8	..	1	6	1	..
Patients with aortic regurgitation						
White						
Males	29	3	5	11	8	2
Females	10	..	3	3	4	..
Colored						
Males	37	2	22	19	14	..
Females	16	4	7	4	1	..
Total						
White	51	3	10	16	16	6
Colored	114	9	42	40	23	..
Males	131	8	41	43	33	6
Females	34	4	11	13	6	..

TABLE 5.—*Average Age of Patients with Aneurysm and Aortic Regurgitation, on Admission to Hospital*

	Average Age, Years					
Diagnostic Group	White Males	White Females	Total White Group	Colored Males	Colored Females	Total Colored Group
Patients with aneurysm (46 yr.)	53	..	53	42	45	43.5
Patients with aortic regurgitation (43 yr.)	46	46	46	44	40	42
Totals*			48			42

* Average age of total number of males, 45 years; females, 41 years.

7 of every 10 cases this suspicion will be verified at necropsy. Equally obviously, the situation is not so serious as this from the clinical standpoint. Many of the pathologic diagnoses of syphilitic aortitis are based on the finding of microscopic lesions in the aortic wall which are not only below the threshold of clinical recognition but also below that of marked physiologic disturbance. The diagnostic issue must be met by careful and reasonably frequent periodic reexamination of all syphilitic patients and by the routine use of fluoroscopic and teleroentgenographic examination of all patients with late syphilis, in order to detect the presence of aortitis at the earliest possible moment. Here, as in the

diagnosis of syphilis itself, the most successful clinicians will be those who possess what Stokes aptly termed a "high index of suspicion."

AGE OF PATIENTS WITH CARDIOVASCULAR SYPHILIS

In table 4 is shown the age on admission of the 165 patients in this series. It is interesting to note that both aneurysm and aortic regurgitation tend to appear at a later age in white males than in other groups. For example, 68 per cent of the white males with aneurysm and 34 per cent of those with aortic insufficiency were over the age of 50, while,

TABLE 6.—*Duration of Infection with Syphilis in Patients with Aneurysm and Aortic Regurgitation*

Diagnostic Group	Total Number of Patients	Number Whose Infection on Admission Was of Duration Given									
		0-5 Yr.	6-10 Yr.	11-15 Yr.	16-20 Yr.	21-25 Yr.	26-30 Yr.	31-35 Yr.	36-40 Yr.	41-45 Yr.	Duration Unknown
Patients with aneurysm.....	53	..	3	6	9	3	4	2	2	1	23
Patients with aortic regurgitation.....	112	2	5	9	18	10	3	4	3	..	58
Total.....	165	2	8	15	27	13	7	6	5	1	81

TABLE 7.—*Average Duration of Infection with Syphilis in Patients with Aneurysm and Aortic Regurgitation*

Diagnostic Group	Average Duration, Years					
	White Males	White Females	Total White Group	Colored Males	Colored Females	Total Colored Group
Patients with aneurysm (21 yr.).....	24	..	..	20	(Insufficient data)	..
Patients with aortic regurgitation (20 yr.)	21	(Insufficient data)	..	19	(Insufficient data)	..
Total*.....		(Insufficient data)	22		(Insufficient data)	20

* The average duration of infection in the total number of males was 20 years.

of Negro males with these conditions, only 20 per cent and 24 per cent, respectively, were over the age of 50. Forty-five per cent of the Negroes were affected before the age of 40, while only 25 per cent of the whites were affected before this age. The majority of the cases occur, as has been repeatedly shown, in the fifth decade of life.

The same data, summarized and rearranged, appear in table 5. Here it is again shown that with both types of lesion, whites are affected later in life than Negroes and males later than females. The explanation of this observation is not clear. That physical stress plays any part seems unlikely, since the youngest group to be affected is that of Negro females. Duration of infection with syphilis may be the responsible factor.

DURATION OF INFECTION AND CARDIOVASCULAR SYPHILIS

Data bearing on this point are presented in table 6 and are summarized in table 7. In almost half the cases no history of early syphilis was obtainable. This was true of most of the women and a few of the men. In 2 patients, aortic regurgitation developed within the first five years of the infection. Sixty-five per cent of the cases occurred between the eleventh and twenty-fifth years of the infection. There is no perceptible difference between the aneurysm and aortic regurgitation groups. The summary in table 7 shows that cardiovascular syphilis tends to develop sooner in Negro males than in white males, and that aortic regurgitation tends to appear in both races a little earlier than aneurysm. These figures suggest that cardiovascular syphilis develops in Negroes at an earlier age than in white patients because they are infected earlier in life. The average age at infection of the two groups in this series is

TABLE 8.—*Duration of Symptoms on Admission (Prior to Treatment) in Patients with Aneurysm and Aortic Regurgitation*

Diagnostic Group	Total Number of Patients	No. Who Had Had No Symptoms*	Number with Duration of Symptoms Given							No. on Whom No Data Were Obtained
			1-12 Wk.	4-6 Mo.	7-9 Mo.	10-12 Mo.	1-2 Yr.	2-3 Yr.	3+ Yr.	
Patients with aneurysm	53	9	12	14	7	4	2	3	1	1
Patients with aortic regurgitation	112	11	36	15	7	12	8	8	6	9
Total	165	20	48	29	14	16	10	11	7	10

* These patients had had no symptoms indicating cardiovascular damage. The lesion was discovered during routine physical examination.

22 and 26, respectively. No adequate data are available for the duration of infection in females of either race.

DURATION OF SYMPTOMS OF CARDIOVASCULAR SYPHILIS

The data showing the duration of symptoms on admission to the clinic and before the institution of treatment are presented in table 8. In 9 patients with aortic aneurysm and 11 with aortic regurgitation there had been no symptoms of any sort pointing to cardiovascular damage. Each of these 20 patients came to the hospital for some other reason, and the lesion was discovered in the course of routine physical examination. No stronger evidence could be presented of the necessity for thorough examination of all patients with syphilis. In the majority of patients, the onset was relatively abrupt, with dyspnea on exertion, paroxysmal noctural dyspnea, pain or even the sudden onset out of an apparently clear sky of congestive heart failure. Such patients quickly sought relief. Not infrequently, however, the onset was insidious and slowly progressive, and in 28 patients (6 with aneurysm and 22 with aortic regurgitation) symptoms had existed for more than a year before the patient came to the hospital. Here the usual story was one of the gradual

appearance of slight exertional dyspnea, which only slowly became more marked or associated with other more alarming symptoms. We have no information as to the extent to which these patients had consulted other physicians before coming to the Johns Hopkins Hospital, but we have the impression that this was not frequent.

From our material nothing can be said as to the time of appearance of physical signs as related to symptoms, age or duration of infection. In all of our patients, characteristic physical signs were present at the time of admission. To answer this question would necessitate the careful following up of a large series of patients with early syphilis over a long period of years.

SOCIAL STATUS AND OCCUPATION

Four patients in this series were from the private practice of one of us (J. E. M.); the remainder were from the semifree clinic of the

TABLE 9.—*Other Lesions of Syphilis Associated with Aneurysm and Aortic Regurgitation*

Cardiovascular Condition	Total Number of Cases	No. in Which Some Other Lesion of Syphilis Was Present	Number in Which the Other Syphilitic Lesion Was of Type Given				
			Central Nervous System	Bone	Skin	Eye	Other
Aneurysm	53	15	9 (2 tabes, 1 dementia paralytica, 2 asymptomatic, 4 meningovascular)	2	4	1	..
Aortic regurgitation	112	29	20 (8 tabes, 3 asymptomatic, 3 vascular, 6 meningovascular)	7	2	..	1 (gumma of larynx)

Johns Hopkins Hospital. Of the 131 males, all except 12 had been engaged in some occupation that demanded considerable physical exertion; and all of the females except one had done their own housework. Only general statements can be made as to the physical and constitutional status of our patients. Except for the presence of cardiovascular syphilis and its complications, most of them appeared to be in remarkably good physical condition. Associated diseases not due to syphilis were uncommon. Most of the men were finely developed muscular persons, apparently in the prime of life.

COINCIDENT SYPHILIS OF OTHER ORGANS

The frequency with which these patients with cardiovascular syphilis were also affected by other syphilitic lesions is shown in table 9. Here is reemphasized the frequent association, so often pointed out, of syphilis of the cardiovascular apparatus and syphilis of the nervous system. Seventeen per cent of the patients with aneurysm and 18 per cent of

those with aortic regurgitation had coincident clinical evidence of neurosyphilis. Curiously enough, late cutaneous lesions occurred in 7.5 per cent of the group with aneurysm but in only 1.7 per cent of the patients with aortic regurgitation; while the reverse relationship was true for late osseous syphilis, which occurred in 3.7 per cent of the group with aneurysm and in 6.2 per cent of that with aortic regurgitation. It is probable that these relationships are only apparent, depend on the relatively small number of cases involved and have no real statistical significance.

THE WASSERMANN REACTION OF THE BLOOD AND THE CEREBROSPINAL FLUID IN CARDIOVASCULAR SYPHILIS

In table 10 appear the figures dealing with the Wassermann reaction of the blood and with the cerebrospinal fluid of the patients under consideration. Of the patients with aneurysm, 98.1 per cent, and of those

TABLE 10.—*The Wassermann Reaction of the Blood and the Results of Tests of the Cerebrospinal Fluid in Patients with Aneurysm and Aortic Regurgitation*

Diagnostic Group	Total Number with Data on Wassermann Reaction Available	Number with Wassermann Reaction of the Blood as Given			Total Number with Data on Cerebrospinal Fluid Available	Number with Reaction of Cerebrospinal Fluid as Given	
		Positive	Doubtful	Negative		Positive	Negative
Patients with aneurysm	52	50	1	1	20	8	12
Patients with aortic regurgitation	111	102	5	4	52	11	41
Total	163	152	6	5	72	19	53

with aortic regurgitation, 96.4 per cent, had a positive Wassermann reaction of the blood. As Carter and Baker [9] pointed out in their survey of similar patients drawn from the same hospital but from a different service, these figures are in excess of many published statistics.

The spinal fluid of our patients with cardiovascular syphilis has not been tested as a routine as has that of our patients with other types of late syphilis. In many instances we have felt that the patient was so ill from his cardiovascular lesion that, whether or not he showed clinical evidence of neurosyphilis, it was unnecessary and unjustifiable to inflict on him the added discomfort of lumbar puncture. The figures shown in table 10 have therefore no real significance, except as they corroborate the clinical diagnoses of neurosyphilis shown in table 9. Elsewhere we have published [16] data showing that the incidence of

16. Moore, J. E., and Faupel, Mildred: Asymptomatic Neurosyphilis: V. A Comparison of Early and Late Asymptomatic Neurosyphilis, Arch. Dermat. & Syph. **18**:99 (July) 1928.

abnormal spinal fluids in 94 patients with cardiovascular syphilis, but without any clinical evidence of involvement of the central nervous system, was 17 per cent. A reasonably accurate estimate of the incidence of neurosyphilis complicating cardiovascular syphilis may be set at from 30 to 35 per cent, by adding the percentage for asymptomatic neurosyphilis (17 per cent) to the percentage of patients in the present series with associated clinical neurosyphilis (17 per cent). Stokes,[17] in his admirable chapter covering a survey of 200 white patients with cardiovascular syphilis, reported that 49 per cent of them had clinical signs of neurosyphilis, and that an additional 5 per cent had abnormal spinal fluids but no signs. Thus, almost one third to one half of all patients with cardiovascular syphilis show clinical or serologic evidence of associated involvement of the nervous system. It may be mentioned in passing that the reverse relationship is still more frequent in certain types of neurosyphilis. Thus, while not all patients with cardiovascular syphilis have tabes, practically all tabetic patients have syphilitic aortitis.

ASSOCIATION OF CARDIOVASCULAR SYPHILIS AND NEUROSYPHILIS AS A COMPLICATING FACTOR IN TREATMENT

The frequent association of cardiovascular syphilis and neurosyphilis often complicates the problem of treatment. One may be hard put to it to decide which is the more important from the patient's point of view. Given, for example, the association of dementia paralytica or tabes dorsalis with optic atrophy and cardiovascular syphilis, to what extent is one justified in subjecting the patient to treatment which is adequate to restore sanity or to prevent or delay loss of vision but which may hasten death from the cardiovascular lesion? Each case is a problem to be decided on its merits. Recently, one of us (J. E. M.) was confronted with the problem of treatment of a private patient with tabes and dementia paralytica (not included in this series) with a manic-grandiose psychosis, rapidly progressing bilateral optic atrophy, syphilitic aortitis with aortic regurgitation, chronic nephritis, hypertension (200 systolic and 120 diastolic), beginning cardiac decompensation and a history of severe postarsphenamine exfoliative dermatitis. The patient's only chance of recovery from the dementia paralytica appeared to lie in fever therapy, tryparsamide being contraindicated because of the optic atrophy. After preliminary digitalization and apparent recovery of cardiac compensation, he was inoculated with malaria. This had to be terminated after six paroxysms because of a rapidly rising nonprotein nitrogen and impending uremia; but after an

17. Stokes, J. H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1926, p. 818.

interval of three weeks, during which these complications disappeared, he was reinoculated and nursed safely through six more paroxysms. Within a month after treatment, he had a complete remission so far as the psychosis was concerned. He was able to leave the psychiatric hospital in which he had been confined, and it is now possible to undertake the further treatment for the cardiovascular features of his illness with measures that would have been utterly ineffective for the neurologic manifestations.

Usually, however, one is faced with a less serious problem, in that the choice of a method of therapy is less for the purpose of dealing with two manifestations of syphilis, either of which will surely be fatal

TABLE 11.—*Type and Amount of Antisyphilitic Treatment Received by Patients with Aneurysm and Aortic Regurgitation Prior to Development of Cardiovascular Syphilis*

Diagnostic Group	Total Number of Patients	Number with History of Infection with Syphilis	Number with No History of Infection with Syphilis	Number Who Had Had No Treatment for Syphilis Prior to Onset of Cardiovascular Lesion	Number Who Had Had Treatment for Given Type of Syphilis Prior to Onset of Cardiovascular Lesion			
					Early Syphilis (No Arsphenamine)	Early Syphilis (Treatment Included Arsphenamine)	Late Syphilis (Treatment Inadequate)	Late Syphilis (Treatment Adequate)
Patients with aneurysm	53	30	23	48	3	1	1	..
Patients with aortic regurgitation	112	54	58	99	8	3	..	2
Total	165	84	81	147	11*	4†	1	2

* In two cases, the administration of mercury (by rubs or by mouth) was continued for from two to three years; in all others, for a few weeks or months only.

† In these cases, the number of injections of arsphenamine for early syphilis was from one to three.

without treatment, than for that of accomplishing the amelioration of distressing symptoms of neurosyphilis by a scheme of treatment that will also be of benefit from the cardiovascular standpoint. Tryparsamide or intraspinal treatment with heterologous arsphenamized serum can sometimes be employed without added risk and with considerable benefit. An intensification of arsphenamine therapy past the point advisable from the standpoint of the circulatory apparatus calls for the most searching scrutiny and careful observation of the patient.

RELATIONSHIP OF PREVIOUS ANTISYPHILITIC TREATMENT TO DEVELOPMENT OF CARDIOVASCULAR SYPHILIS

We have pointed out that reasonably adequate treatment for early syphilis appears to protect the patient against a subsequent development of cardiovascular syphilis. In table 11, we approach this important ques-

tion from another angle, that of the amount of treatment for syphilis received by the patients in this series before the development of cardiovascular damage. For the sake of completeness, we reemphasize the fact that only 30 of the 53 patients with aneurysm and 54 of the 112 with aortic regurgitation gave any history of possible early manifestations of the infection. Practically all of the remaining 81 patients (49 per cent) had no idea that they had syphilis until the diagnosis was made at the time of their admission to the hospital for cardiovascular syphilis. This includes almost all of the 34 women in the series, and also a large number of the men. Stokes,[17] dealing with an exclusively white clientele, found that one third of his 200 patients with cardiovascular syphilis could give no history of infection. Symptomless infection, now demonstrated in animals,[18] or infections with insignificant chancres and an absent or unobtrusive secondary outbreak, must be nearly as common in patients in whom cardiovascular syphilis subsequently develops as in those who fall victims to neurosyphilis. In any large series of patients with cardiovascular syphilis, therefore, one can expect that from one third to one half of the patients will never have received any previous treatment, because they will have been unaware that they were infected.

It is startling to note, however, that in our material only 15 of the 84 patients who gave a history of early syphilis had ever taken any treatment for it. Of these, 11 had had only mercury, and only 2 of the latter group had continued this form of therapy for what was felt, in the prearsphenamine days, to be an adequate length of time. Nine had taken the drug for a few weeks or months only, stopping because they thought themselves cured. Four patients had received from one to three injections of an arsphenamine product at the time of their infection. Not a single patient in this whole series had received as many as six injections of arsphenamine for early syphilis. These figures are in striking corroboration of the opinion that adequate early treatment prevents the development of cardiovascular damage. Three additional patients had been treated before their admission for neurosyphilis, the cardiovascular lesion either having been overlooked or having subsequently developed. Two of these had received as many as two courses of treatment with arsphenamine with interim treatment with heavy metal compounds.

One hundred and forty-seven patients (89 per cent) had never received treatment for syphilis.

These data, with the figures given in an earlier paragraph as to the incidence of cardiovascular syphilis in patients receiving varying amounts

18. Kolle, W.: Ueber symptomlose Infektionen und ihre Bedeutung für Epidemiologie, Pathologie, und Immunität, insbesondere der Syphilis, Schweiz. med. Wchnschr. **59**:517, 1929.

of treatment for early syphilis at our hands, have an important bearing on the controversy taking place, especially in Germany, over the apparently increased incidence of syphilitic aortitis since the introduction of arsphenamine. Langer's important paper [14] provides a discussion of this disputed point. He and others concluded that there has been a striking increase in the incidence of syphilitic aortitis as observed at necropsy during the past fifteen years. Our material indicates, first, that the vast majority of all patients with cardiovascular syphilis have never been previously treated; second, that a relatively small amount of arsphenamine appears to protect the patient against the development of cardiovascular damage. Our feeling is that the increased incidence is more apparent than real and is based on increasingly accurate pathologic study and a more intimate knowledge of the microscopic lesions of syphilitic aortitis.

THE LITERATURE ON THE TREATMENT OF CARDIOVASCULAR SYPHILIS

We have not attempted a detailed review of the literature on the treatment for cardiovascular syphilis, chiefly because there are few reports with the material of which ours may be compared. It is difficult, if not impossible, to obtain from the older literature any clear idea of how often or to what extent actual benefit occurred. Most writers on the subject (and this criticism applies also to the more modern writers) discuss the prognosis and outcome in "cardiovascular syphilis" or in "syphilitic aortitis" without differentiating the clinical material further. Obviously, the prognosis and the results to be expected from treatment should be better in the stage of simple aortitis than after the development of aortic insufficiency or of aneurysm; and in the latter two conditions, better before than after the appearance of manifest myocardial failure. Many of the older clinicians, and more recent authors as well, advocate one or another method of treatment, or advise against treatment, on the basis of their opinions, failing to detail the facts on which their opinions are based. Others describe the results of treatment in a small number of cases. To draw conclusions from individual instances of apparent therapeutic success or failure, or to consider a few cases only, no matter how carefully studied, is a dangerous procedure in a condition in which progress without treatment is so variable as in cardiovascular syphilis. The only fair method of approach to the problem is by the statistical study of a larger number of comparable cases.

We have been able to find four papers in which data are presented in some degree comparable with our own. In 1919, Reid [19] reported the results of treatment in 61 patients with syphilitic aortitis, of whom 43

19. Reid, W. D.: Prognosis of Specific Aortitis, J. A. M. A. **73**:1832 (Dec. 13) 1919.

presumably had aortic regurgitation. He was able to follow only 22 of these patients, but concluded that with proper treatment symptoms were alleviated and life definitely prolonged. It is not possible to be sure how many of his followed patients had simple aortitis or aortic insufficiency, and the numbers involved are too small for statistical accuracy as to prolongation of life.

Cotton,[20] in 1926, discussed the ultimate outcome in 107 patients with aortic regurgitation, of whom 7 also had aortic aneurysm. Fifty-two of this group were given no antisyphilitic treatment and were used as controls. The remaining 55 were treated with courses of neoarsphenamine and mercury. The author is not clear as to how much treatment was given, though it is implied that all of the treated patients received a course of each drug once a year for five years. He said that both the untreated and the treated groups were given the same type of general medical care, and that they were observed over a five year period. Presumably, at the end of this period, 34 of the 52 untreated patients were still living and 18 were dead, a mortality of 34 per cent. Of the 55 treated patients, 41 were still living and 14 dead, a mortality of 25 per cent. Thus treatment appeared to offer a 9 per cent increased chance of survival for the period of observation. It is unfortunate that Cotton did not define more accurately the duration of life in treated and untreated patients. On the basis of our own material and that of other observers the world over, it is difficult to believe that 34 of the 52 untreated patients with aortic regurgitation survived for a full five years, since it is generally agreed that the average duration of life after the onset of symptoms in untreated patients with aortic regurgitation is from one to two years (Scott).[21] The value of Cotton's paper is much impaired by this omission and by his failure to provide more accurate details of the treatment given.

Conybeare [22] reported on the effect of treatment in aortic aneurysm. His series was small, consisting of only 23 patients, but his data are well presented. Twelve patients, serving as controls, received no antisyphilitic treatment. Of these, 4 were living at the time of the report, the average duration of life from the onset of symptoms being forty-five months; 8 were dead in an average period of ten months. Eleven patients were treated with varying amounts of neoarsphenamine. Only 2 of these received much treatment, the remaining 6 all being given from one to eight injections of the drug. In spite of this relatively

20. Cotton, F. F.: Cardioaortic Syphilis and Its Treatment, Brit. M. J. **1**:855, 1926.

21. Scott, R. W.: Syphilitic Aortic Insufficiency, Arch. Int. Med. **34**:645 (Nov.) 1924.

22. Conybeare, J. J.: The Treatment of Aortic Aneurysm by Anti-Syphilitic Remedies, Guy's Hosp. Rep. **74**:163, 1924.

small amount of treatment, 7 of the treated patients were still living over an average period of forty months from the onset of symptoms, and 4 of these were symptom-free and able to do hard physical labor. Four were dead in an average period of thirty months. On the basis of these figures, Conybeare was convinced of the value of neoarsphenamine in aortic aneurysm.

Recently, Herrmann and Jamison [23] discussed the outcome of treatment in 100 patients with aortic regurgitation, all of whom had had congestive heart failure before treatment was started. Unfortunately, these authors subdivided their material into small groups and attempted a simultaneous but not interrelated analysis of the effect of varying amounts and types of antisyphilitic treatment and the effect of such various measures to relieve congestive heart failure as ouabain, large versus small doses of digitalis, etc., so that it is difficult, if not impossible, for the reader to unravel the significance of their figures. Disregarding all features of their report except that dealing with antisyphilitic treatment, and rearranging their figures for the sake of simplicity, one finds that 40 patients received little or no treatment, of whom 12 were living and 28 dead at the date of reporting, a mortality of 70 per cent. Fifty-eight patients were given what we should regard as a moderate amount of treatment (corresponding roughly to the treatment given our groups 2 and 3, subsequently to be described); of these, 26 were living and 32 dead, a mortality of 55 per cent. It is impossible to extract from this paper any quotable details as to the average duration of life in the various groups. The authors concluded, however, that antisyphilitic treatment definitely prolongs life, and that, while living, treated patients are usually much more comfortable than those who are untreated. Herrmann and Jamison properly laid great stress on the prognostic importance of congestive heart failure and the necessity for adequate supportive treatment from the standpoint of the circulation.

EVOLUTION OF A METHOD OF TREATMENT FOR CARDIOVASCULAR SYPHILIS

The past twenty years have seen three almost complete revolutions in the attitude of physicians toward the treatment for cardiovascular syphilis. Before the introduction of arsphenamine, it was generally agreed that some benefit could be obtained from the judicious use of mercury alone, mercury with iodides or the iodides alone. Symptomatic improvement occurred often with a combination of these treatments,

23. Herrmann, G., and Jamison, C.: The Treatment of Cardiovascular Syphilis with Especial Reference to Aortic Regurgitation with Congestive Heart Failure, Am. J. Syph. **15**:1, 1932.

and many able clinicians were convinced that, at least in individual cases, life was prolonged.

After the introduction of arsphenamine, and in spite of the original cautions against its use in patients with damaged hearts, it was almost as universally applied to the treatment of patients with syphilitic heart disease as to the treatment of those with late syphilis of all types. At this point, our experience in the management of cardiovascular syphilis began. The results of this indiscriminate use of a powerful drug were disastrous. It was found that when the drug was given in average therapeutic dosage to ambulant patients, sudden death might occur during the injection. Such reactions were characterized by fainting, ashy gray-green pallor and profuse sweating; the pulse became rapidly imperceptible; the patient gave a few gasps and died. At least four such deaths occurred in our own clinic.

Electrocardiographic studies by Reid [24] and by Wilson, Wile, Wishart and Herrmann [25] have an important bearing on the mechanism of this type of reaction. Each of these observers gave arsphenamine in average therapeutic doses (from 0.3 to 0.4 Gm.) to patients with syphilitic heart disease, obtaining electrocardiographic records before and shortly after the injection. Reid observed changes that he interpreted as a prolongation of conduction time and a shortened refractory period of the muscle. He concluded that in a heart which is damaged by syphilis, and which is in "a bad metabolic state," these two changes predispose to the occurrence of ectopic ventricular tachycardia or to ventricular fibrillation, the latter of which is, of course, suddenly fatal. Wilson and his co-workers likewise noted abnormal idioventricular rhythm and diphasic complexes suggesting incomplete bundle branch block, and concluded that, in cardiovascular syphilis, the administration of arsphenamine may sometimes be followed by myocardial changes of an undesirable kind.

A second type of disastrous outcome was sudden death within from twenty-four to forty-eight hours after the injection of the drug, due to therapeutic shock (Jarisch-Herxheimer reaction). Usually this was due to sudden coronary occlusion or to rupture of an aneurysm. Still a third untoward effect was the sudden appearance of congestive heart failure in patients whose cardiac compensation had been adequate before treatment. This was emphasized by Wile [26] as "the therapeutic paradox."

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24. Reid, W. D.: The Mechanism of the Toxic Action of Arsphenamine on the Heart, J. A. M. A. **84**:883 (March 21) 1925.

25. Wilson, F. N.; Wile, U. J.; Wishart, S. W., and Herrmann, G. R.: Changes in the Electrocardiogram Following the Arsphenamine Treatment of Cardiac and Aortic Syphilis, Proc. Soc. Exper. Biol. **23**:275, 1926.

26. Wile, U. J.: The Treatment of the Syphilitic Liver and Heart: A Therapeutic Paradox, Am. J. M. Sc. **164**:415, 1922.

He attributed the phenomenon to the rapid healing of syphilitic inflammatory tissue in the aortic wall, valve cusps or myocardium, which is then replaced by contracting scar tissue. This brings about anatomic healing, but leaves the patient functionally worse than before treatment. The early current favorable opinion as to the beneficial effect of treatment with arsphenamine, summarized by Longcope,[27] was more than counterbalanced by the ill effects just described.

For a time, the pendulum swung back, and it was generally thought that, since the danger of treating patients with cardiovascular syphilis was far greater than the improvement to be expected, it was better to give no antisyphilitic treatment or, if any, mercury and potassium iodide only, as in the prearsphenamine era. We shared in this feeling of pessimism, and for several years our patients received no treatment other than the usual medical measures of rest, diet, digitalization and restriction of activity. Patients so treated constitute a large part of our control material, shortly to be described.

The World War was partly responsible for the inauguration of the plan of treatment of persons with cardiovascular syphilis which we now employ, and which, subject to various modifications, has been independently evolved by many other observers.[28] Neoarsphenamine became popular during the war years because of its ease of administration. It was found to be less prone to produce minor reactions in average therapeutic doses than arsphenamine and in small dosage to be practically free from any after-effect. This led to its trial cautiously in patients with cardiovascular syphilis, and it was generally found that with proper precautions such patients could tolerate small doses (from 0.1 to 0.3 Gm.) without the dangers of sudden death from ventricular fibrillation or from therapeutic shock. The measures taken to avoid the latter disaster, namely, several months of preliminary treatment with mercury and the iodides in order to promote slow rather than rapid resolution

27. Longcope, W. T.: Syphilitic Aortitis: Its Diagnosis and Treatment, Arch. Int. Med. **11**:15 (Jan.) 1913.

28. Braun, L.: Ueber die Behandlung der syphilitischen Herz- und Gefässkrankheiten, Wien. med. Wchnschr. **77**:122 and 150, 1927. Goldberg, B. I.: The Value of Specific Treatment in Cardiovascular Syphilis, Boston M. & S. J. **193**:768, 1925. Herrmann and Jamison (footnote 23). Hines, L. E., and Carr, J. G.: The Use of Intravenous Arsenicals in the Treatment of Cardiovascular Syphilis, Am. Heart J. **6**:142, 1930. Horder, T.: Syphilis of the Heart and Aorta and Its Appropriate Treatment, Brit. J. Ven. Dis. **2**:117, 1926. Scherber, G.: Die Behandlung der verschiedenen Formen der syphilitischen Mesaortitis, Dermat. Wchnschr. **92**:56, 1931. Schlesinger, H.: Die Behandlung der Mesaortitis im Stadium der Dekompensation, Wien. klin. Wchnschr. **43**:562, 1930. Schottmüller, H.: On the Treatment of Syphilis of the Aorta, Am. J. Syph. **9**:1, 1925. Stokes (footnote 17, p. 850). Symposium (Citron, Galewsky, Kisch, Leschke, Ritter, Schlesinger): Indikationen und Erfolge der spezifischen Therapie bei Aorten Syphilis, Dermat. Wchnschr. **92**:19, 1931.

of syphilitic inflammatory tissue, were also found to be of value in preventing the therapeutic paradox. The introduction of bismuth provided another drug free from dangerous after-effects and therapeutically more active than mercury. From the accumulated experience with the use of these drugs, in combination with the older medical measures, has evolved the rather elastic treatment scheme which we now describe.

If, on admission, the patient has any evidence of congestive heart failure, he is promptly put at complete rest in bed and is digitalized. Diet and fluid intake are restricted. If there is no edema, antisyphilitic medication, except for the iodides, is omitted until compensation has been regained. If edema is present, one of the soluble mercurial salts (for example, succinimide intramuscularly or salyrgan intravenously) may be employed for a few days for its combined diuretic and antisyphilitic effect. As Brooks [29] and also Carter and Baker [8] pointed out, patients with cardiovascular syphilis, especially Negroes, seem to be more refractory to digitalis than those with other forms of cardiac failure, and even large doses sometimes fail to produce any physiologic effect. Rest in bed is prolonged, if possible, until well after compensation has been recovered; convalescence is purposely slow, and graduated exercise is rigorously supervised. On discharge from the hospital, restriction of activity is insisted on, often necessitating a change of occupation from manual labor to a sedentary position requiring a minimum of physical exertion. The patient is warned against sudden physical strain of any type. Powdered digitalis, in a dosage of from 0.1 to 0.2 Gm. daily, is given to ambulant patients with a low cardiac reserve over indefinite periods of time, sometimes continuously. For anginal pains or substernal discomfort, the nitrites and a mixture containing theobromine and phenobarbital have proved helpful. Careful watch is kept for an impending repetition of cardiac failure, and if symptoms appear, rest in bed is immediately reinstituted. Encouragement is essential, and it is often wise to conceal the gravity of the situation from the patient, at the same time notifying a responsible member of the family of a possible unfortunate outcome.

Antisyphilitic treatment, usually with intramuscular injection of an insoluble bismuth salt combined with the administration of potassium or sodium iodide by mouth, is started as soon as a fair degree of cardiac reserve has been established. The dosage of bismuth is usually small at first—0.1 Gm. every four or five days. If this is tolerated for four or five injections without an upset, as is ordinarily the case, the dose is increased to 0.2 Gm. once a week. At the start of treatment, we believe that insoluble bismuth salts are preferable to soluble salts, because of their slower absorption, and preferable to mercury by any route because

29. Brooks, H.: The Treatment of Cardiovascular Syphilis, Warthin Anniversary Volume, Ann Arbor, Mich., George Wahr, 1927, p. 117.

of their lower toxicity and more certain therapeutic effect. The dosage of the iodide is usually 1.3 Gm. three times a day, increasing rapidly to 4 Gm. three times daily. Larger doses than these appear to be unnecessary. This type of treatment with bismuth and the iodides is continued for at least from ten to twelve weeks before any arsphenamine product is given. Indeed, in some patients who never succeed in establishing a satisfactory degree of cardiac reserve, the use of any arsenical drug is omitted, and treatment carried on with courses of bismuth and the iodides alternating with rest periods of from two to four months, or with courses of mercury by inunction. If, on completion of the first course of bismuth, the patient has not sufficiently recovered compensation as to be completely ambulatory without the persistence of slight edema or some exertional dyspnea, the arsenical drug of choice is bismarsen (bismuth arsphenamine sulphonate). This preparation is administered intramuscularly in a dosage of first from 0.05 to 0.1 Gm. not oftener than every five days, and later, if no reactions occur, 0.2 Gm. every four to seven days. A course of bismarsen consists of from twelve to twenty injections. If, on the other hand, the patient is able to be ambulatory with only slight or no symptoms of cardiac embarrassment, neoarsphenamine administered intravenously, is employed. The initial dosage is again minute, from 0.05 to 0.1 Gm., and is cautiously increased at weekly intervals and by gradual steps until the usual maximum dose of 0.3 Gm. is reached. In rare instances, when patients are symptomless, this maximum may be exceeded, and 0.45 or 0.6 Gm. given. The aim of treatment is, however, to avoid reactions of any kind; hence the larger dosage of neoarsphenamine, and the use of old arsphenamine particularly, are avoided. A course of neoarsphenamine consists of from ten to twelve injections. Whenever possible, treatment is continued by this system of courses of bismuth and the iodides alternating with courses of neoarsphenamine in small dosage, without rest periods of any kind, for an indefinite period of time, and certainly for a minimum of two years. After two years of continuous treatment, if the patient's general physical condition is satisfactory, it is permissible to institute long periods of rest. It is probably wise to give an occasional course of bismuth followed by one of bismarsen or neoarsphenamine, say perhaps once a year, for the duration of the patient's life. The minimum requirement of two years of treatment has been arbitrarily set, based on the clinical progress of the patients reported on in this paper. No attention is paid to the response of the Wassermann reaction of the blood to treatment, since Wassermann fastness is the rule.

Whether it is advisable to attempt this treatment régime or to limit one's self to medical measures for the relief of symptoms only depends on many collateral factors, such as age, general physical con-

dition and presence of a complicating disease. Six patients in the present series were over the age of 60, and recently we have seen 2 patients, aged 72 and 81, respectively, in whose cases the diagnosis of syphilitic aortic regurgitation seemed certain. Here it is obviously undesirable to do much more than to give mercury by mouth. The presence of severe impairment of renal function may preclude the use of mercury or of bismuth in any form, and one's sole reliance must be placed on bismarsen or on neoarsphenamine.

Complicating neurosyphilis, especially tabes dorsalis or dementia paralytica, may call for special measures of treatment, including the use of tryparsamide, which fortunately seems to exercise no deleterious effect on the cardiovascular lesion, of intraspinal therapy (usually with heterologous serum) for the relief of optic atrophy or intractable lightning pains or, in desperate situations, of fever therapy. Wile [30] advocated tryparsamide instead of any of the arsphenamines in selected cases of cardiovascular syphilis, whether or not a complicating neurosyphilis is present. He expressed the belief that it may exercise a direct beneficial effect on the cardiovascular lesion. As we shall subsequently indicate, we disagree with this point of view, and think that this drug is of little or no value in any type of syphilis except that in which there is involvement of the central nervous system. Each patient presents a problem differing from that of every other, and there is no field of syphilotherapy in which the art of medicine needs to be exercised so much as in cardiovascular syphilis.

With this general statement of principles of treatment, we proceed to a consideration of the results obtained in the 165 patients comprising the material of this paper. Limitations of space prevent any consideration of individual cases; our results must be presented entirely in statistical form. Indeed, as we have emphasized, this is the only satisfactory method of presentation, since the course of the disease in any individual patient is so variable as to make conclusions untrustworthy.

THE METHOD OF STUDY

The files of the Syphilis Division include the records of a few more than 300 patients with aneurysm or aortic regurgitation. Those patients who had disappeared from observation were written to and visited by social service workers. When located, they were urged to return to the clinic for examination or, when this was impossible, to provide detailed information as to their present state of health. Reports of death were obtained from family physicians, relatives or neighbors, from the files of the Johns Hopkins Hospital, the Municipal Hospital

30. Wile, U. J.: Principles Underlying the Treatment of Cardiovascular Syphilis, Am. Heart J. **6**:157, 1930.

and the five largest of the other hospitals in Baltimore, and by an examination of the death certificates at the Baltimore City Health Department. The study was completed on July 1, 1931. By that date, it had been possible to trace the ultimate outcome in 165 patients, or more than half of those whose records were in the files. One hundred and nine of these were dead; of the remainder, all were still under observation on July 1, 1931, except 3. These are included in the series and classified as living because they were followed for periods of time ranging from six to eleven years and were living and in good condition when last seen.

In this paper, we review and augment the data as to ultimate outcome in terms of "living and dead" presented in our preliminary paper. At the same time, we have analyzed the material from several other standpoints that we hope will aid in an understanding of what treatment actually accomplishes.

RESULTS OF TREATMENT IN PATIENTS WITH AORTIC ANEURYSM

In table 12 are presented the data as to the effect of treatment on the prolongation of life in 53 patients with aneursym of the aorta. Nine of these patient also had aortic regurgitation. In all instances except one, the diagnosis was based on physical signs and on the presence of a characteristic sacculated aneurysm of the thoracic aorta at fluoroscopic and teleroentgenographic examination. The excepted instance was that of a patient with an easily palpable aneursym of the abdominal aorta, the presence of which was confirmed by exploratory operation. Symptoms, however, were absent in 9 patients, a fact to which subsequent reference will be made.

In table 12 and those following, the patients are divided into four groups on the basis of the amount of treatment received. Group 1 includes those patients who received little treatment or none. "Little treatment" means a few weeks of treatment with mercury (by inunction or by mouth), an injection or two of an arsphenamine product or a few injections (less than eight) of bismuth. Group 2 includes patients who received the equivalent of one course of an arsenical drug (from six to eight injections) or one long course (from twelve to sixteen injections) of a heavy metal, either bismuth or mercury. This amount of treatment was usually given over a period of from one and one half to four months. In group 3 are patients who received the equivalent of one long course each of an arsenical drug and of a heavy metal, occupying from four to twelve months' time. Group 4 includes all patients treated for more than one year. This involved a minimum of two long courses each of an arsphenamine product and of a heavy metal or four long courses of a heavy metal alone. Many patients in

this group, however, had been more or less continuously treated for several years, and had received from eight to ten courses each of an arsenical drug and of bismuth or mercury.

It is important to note that although the 165 patients studied differed in the amount of antisyphilitic treatment received, they were all treated when necessary by the usual medical régime of rest, diet, digitalis, restriction of activity, etc. In this respect, the patients of our treatment group 1 were as well managed as those in group 4. The only essential difference in the treatment received by the patients in these four groups was in the amount of specific treatment for syphilis. It is perfectly fair, therefore, to attribute any difference observed in course or ultimate outcome to this factor, and to no other.

TABLE 12.—*Effect of Treatment on Prolongation of Life in Patients with Aneurysm of the Aorta*

Treatment Group	Number of Patients in Group	Number Living	Number Dead	Average Duration of Life Until Death or Last Observation, Dating from	
				Onset of Symptoms	Start of Treatment
Group 1. Patients with no treatment or very little	22	2	20	19 mo.	14 mo.
Group 2. Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	10	2	8	51 mo.	45 mo.
Group 3. Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	6	3	3	67 mo.	43 mo.
Group 4. Patients treated for more than 1 year: two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	15	9	6	75 mo.	63 mo.

The duration of life is measured as dating (*a*) from the onset of symptoms and (*b*) from the start of treatment, until death or the date of the last observation. This distinction is drawn in order to point out, as will be shown later in another way, that the patients with an unfavorable outcome are not necessarily those who had been ill for the longest time before starting treatment.

The data given in table 12 need no detailed explanation. Of 22 patients who received little or no treatment, 2 are now living and 20 are dead, a mortality of 90 per cent. The average interval of time until death, dating from the onset of symptoms, was only 16 instead of 19 months. The discrepancy between this statement and the table is due to the fact that the two living patients have now lived for 52 and 66 months, respectively, after the onset of symptoms. Had these two patients been treated, one would have been inclined to attribute their

apparent longevity to the effects of treatment; this emphasizes our frequently repeated statement that one can draw no trustworthy conclusions from the behavior of the individual case. In the 20 dead patients in group 1, the duration of life from the onset of symptoms ranged between the extremes of 3 and 43 months. Thirteen of them died within one year. Lucke and Rea [31] quote several authorities who believed that the duration of life after the clinical recognition of aneurysm varies between 12 and 30 months (no distinction being made between treated and untreated patients).

Contrast this gloomy picture with that of the 15 patients who were treated for more than a year (group 4). Of these, 9 are living and 6 are dead, a mortality of 40 per cent. The average duration of life has

TABLE 13.—*Effect of Treatment on Prolongation of Life in Patients with Aortic Regurgitation*

Treatment Group	Number of Patients in Group	Number Living	Number Dead	Average Duration of Life Until Death or Last Observation, Dating from	
				Onset of Symptoms	Start of Treatment
Group 1. Patients with no treatment or very little	57	5	52	30 mo.	23 mo.
Group 2. Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	16	4	12	23 mo.	15 mo.
Group 3. Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	14	10	4	46 mo.	37 mo.
Group 4. Patients treated for more than 1 year: two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	25	21	4	64 mo.	53 mo.

risen from 19 to 75 months from the onset of symptoms. The 9 surviving patients have lived for an average of 88 months: the remaining 6 died at an average of 48 months after the appearance of symptoms. The actual durations of life in the living patients are (to July 1, 1931) 18, 46, 52, 68, 72, 98, 132, 144 and 156 months, respectively; in the dead patients, 12, 23, 48, 72, 87 and 97 months, respectively.

The figures for patients in treatment groups 2 and 3 indicate that even a little treatment aids in the prolongation of life. If one adds them together as an intermediate group between the untreated or practically untreated patients of group 1 and the well treated patients of group 4, the figures are as follows: of 16 patients, 5 are still living and 11 are dead, a mortality of 68 per cent. The average duration of

31. Lucke, B., and Rea, M. H.: Studies on Aneurysm: I. General Statistical Data, J. A. M. A. **77**:935 (Sept. 17) 1921.

life, dating from the onset of symptoms, is, in the 5 living patients, 72 months; in the 11 dead patients, 44 months.

EFFECT OF TREATMENT ON PROLONGATION OF LIFE IN PATIENTS WITH AORTIC REGURGITATION

An identical presentation of data for 112 patients with aortic regurgitation appears in table 13. Again contrast the untreated patients of group 1 with the well treated patients of group 4. Of the 57 patients in group 1, 5 are living and 52 are dead, a mortality of 91 per cent. The average duration of life for the whole group, dating from the onset of symptoms, was 30 months. For the 52 dead patients, death followed the appearance of symptoms in an average of 27 months. Fourteen died within the first year, 15 in the second year, 7 in the third, 5 in the fourth and 7 in the fifth. Three lived for more than 5 years after symptoms first developed. The extremes of duration of life were 1 month and 78 months, respectively. In the 5 patients in this group still alive, the duration of life from the onset of symptoms until the present has been 36, 54, 66, 72 and 134 months, respectively, an average of 72 months. Here again yawns the pitfall of misinterpretation of the value of therapy on the basis of individual instances. These 5 patients, all untreated, have lived fairly comfortably for a time far greater than the average.

Now compare these data and the mortality of 91 per cent with the corresponding data and mortality of group 4. Of these 25 well treated patients, 21 are still living and 4 are dead. The mortality is 16 per cent. The 4 dead patients died in an average of 28 months after symptoms appeared. The 21 living patients have lived for an average period of 71 months (extremes, 24 and 159 months). The living patients have so far lived no longer, on the average, than those still living in group 1; but there are far more of them (84 per cent as compared with 9 per cent of the respective groups).

The duration of life in untreated patients with aortic regurgitation is longer than in those with aneurysm of the aorta—27 as compared with 16 months; and the average prolongation of life obtainable in well treated patients with the former condition is distinctly less. It is also worth noting, though the number of cases of both types is too small for one to be sure, that apparently a little antisyphilitic treatment has a distinctly harmful effect on patients with aortic regurgitation, as compared with its apparently beneficial effect on those with aneurysm; in this series, in the patients with aortic insufficiency in group 2 the average duration of life was actually less than that in the group in which no treatment was given. This is probably a reflection of the relationship of congestive heart failure to the ultimate outcome, a point presently discussed in detail.

EFFECT OF TREATMENT ON PROLONGATION OF LIFE IN PATIENTS WITH CARDIOVASCULAR SYPHILIS

When these data were incompletely presented at the meeting of the American Heart Association, an eminent physician commented in discussion [32] on the possibility that this and other studies reported were not statistically significant because the number of observations was so small and the probable error so great. It hardly needs emphasis that it is difficult for any single group of observers to collect a large series of adequately studied and followed cases of cardiovascular syphilis. So far as we are aware, the material of the present paper is the largest available. It has occurred to us that statistical accuracy might be better

TABLE 14.—*Effect of Treatment on Prolongation of Life in Whole Group of Patients with Cardiovascular Syphilis (Aneurysm and Aortic Regurgitation)*

Treatment Group	Number of Patients in Group	Number Living	Number Dead	Average Duration of Life Until Death or Last Observation, Dating from	
				Onset of Symptoms	Start of Treatment
Group 1. Patients with no treatment or very little	79	7	72	27 mo.	21 mo.
Group 2. Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	26	6	20	33 mo.	26 mo.
Group 3. Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	20	13	7	46 mo.	39 mo.
Group 4. Patients treated for more than 1 year: two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	40	30	10	68 mo.	57 mo.

served if we grouped together as presenting cardiovascular syphilis all of our patients with aortic aneurysm and aortic regurgitation. The two conditions have many things in common, and this use of the material, by providing larger numbers in each of our treatment groups, decreases the probable statistical error. This has accordingly been done in table 14. Since the two preceding tables have been analyzed in the text, the data of table 14 are allowed to stand without detailed explanation.

The question as to whether these figures actually are statistically significant was submitted to L. J. Usilton, statistician of the United States Public Health Service. She replied [33] that this could be deter-

32. Emerson, Haven, in discussion of paper by Wile, U. J.: Am. Heart J. 6:161, 1930.

33. Usilton, L. J.: Personal communication.

mined only from a knowledge of the total number of cases in each treatment group, from which the reported material was drawn. When this was investigated, it was found, for example, that there were 128 patients with cardiovascular syphilis in treatment group 1, of whom we had been able to trace only 79 until death or the present time; while of a total of 45 cases in treatment group 4, we had succeeded in tracing 40. To paraphrase Usilton's comment, "If one considers that the end-result is known in 89 per cent of group 4 and in only 61 per cent of group 1, the probabilities are that adequate treatment prolongs the life of the individual with cardiovascular syphilis. Further, the pro-

TABLE 15.—*Effect of Treatment on Prolongation of Life in Patients with Cardiovascular Syphilis, Computed on Living and Dead Patients Separately*

Treatment Group	Number of Patients in Group	Number Living	Average Duration of Life to Last Observation, Dating from: Onset of Symptoms	Average Duration of Life to Last Observation, Dating from: Start of Treatment	Number Dead	Average Duration of Life to Death, Dating from: Onset of Symptoms	Average Duration of Life to Death, Dating from: Start of Treatment
Group 1. Patients with no treatment or very little	79	7	68 mo.	67 mo.	72	23 mo.	16 mo.
Group 2. Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	26	6	62 mo.	52 mo.	20	25 mo.	19 mo.
Group 3. Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	20	13	45 mo.	36 mo.	7	49 mo.	44 mo.
Group 4. Patients treated for more than 1 year: two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	40	30	76 mo.	66 mo.	10	45 mo.	30 mo.

longation of life is placed at a minimum in the 68 months shown for group 4, because the termination of life has not yet occurred in 30 of the 40 persons in this group; whereas only 7 of 79 patients are still living in group 1, and yet the average life period from the onset of symptoms is 27 months." In other words, the average duration of life for patients in group 1 cannot be greatly affected no matter how long the surviving 7 patients may live, while the longer the surviving 30 patients of group 4 continue to live, the greater the increase of the average duration of life in this group. There can be no doubt, we believe, that our data are statistically significant.

An attempt to solve this difficulty in another way is shown in table 15. Here we show the duration of life for living and for dead patients separately. With the duration of life measured from the onset

of symptoms, it appears that in the living patients there is little or no significant increase in the duration of life corresponding to whether the patients were untreated or well treated. The probable explanation for this is that the period of time covered by the study is roughly the past ten years, and that not enough time has elapsed to bring out a difference even in the two extreme groups. So far as living patients are concerned, we must at present stand on the fact that the percentage probability of survival for the period of observation is in direct proportion to the amount of treatment given, i. e., for group 1, 8 per cent; group 2, 23 per cent; group 3, 65 per cent; group 4, 75 per cent.

If one turns to the patients now dead, however, it seems fairly definite that, even though the outcome was death, the duration of life was approximately doubled by good treatment as compared with little or none.

RELATIONSHIP OF DURATION OF SYMPTOMS AND OF CONGESTIVE HEART FAILURE TO THE OUTCOME OF TREATMENT IN CARDIOVASCULAR SYPHILIS

An obvious objection that may be leveled at the conclusions that we have so far drawn is that the material in the various treatment groups is not comparable, that the more seriously ill patients are those who died, and that the survivals represent patients with less serious or less rapidly progressive lesions. We have attempted to view our material critically from this standpoint. Since we avoid placing undue emphasis on the individual case, we have taken as our criteria of relative seriousness, first, the average duration of symptoms in the various treatment groups; second, the number of patients who were symptom-free before treatment was begun, and third, the number who had and the number who did not have congestive heart failure before or after treatment. These data appear in table 16. Patients with aneurysm and those with aortic regurgitation are grouped as patients with cardiovascular syphilis in this and most of the subsequent tables, since there are no significant differences between the two groups.

The term "duration of symptoms" refers here, as elsewhere in this paper, to the length of time during which the patient has suffered from one or more of the commonly accepted symptoms of cardiovascular syphilis. It will be noted that there are no important differences in the various treatment groups. Certainly, it is not true that the well treated patients, with only 25 per cent dead, had had symptoms for a much shorter period of time than the untreated group, with 89 per cent dead. Indeed, the reverse appears to be the case.

It might *a priori* be supposed that patients who had never had any symptoms, the existence of the lesion being accidentally discovered at routine examination, were particularly suitable subjects for treatment.

That this is usually, but not always, true is indicated by the fact that 11 of 20 such patients are living, while 9 are dead. One of these died of sarcoma, another of miliary tuberculosis, and the remaining 7 of cardiovascular syphilis. Among the 11 surviving patients originally symptom-free, 7 are still perfectly well and working, no symptoms having developed. In the remaining 4, symptoms have appeared in spite of treatment; 2 of these are, however, still able to do light work, and 2 are incapacitated by the progress of their disease.

TABLE 16.—*Relationship of Duration of Symptoms and of Cardiac Failure to Outcome of Treatment in Patients with Cardiovascular Syphilis*

Treatment Group	Total Number of Patients	Average Duration of Symptoms Before Treatment	Number of Patients Symptomless Before Treatment	Number Who Did Not Have Cardiac Failure		Number Who Had Cardiac Failure		No. on Whom No Data Was Obtained as to Cardiac Failure	
				Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Group 1. Patients with no treatment or very little									
Living	7	2 mo.		6	2	1	2		3
Dead	72	9 mo.	5	30	10	41	29	1	33
Group 2. Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)									
Living	6	14 mo.	2	6	2		4		
Dead	20	7 mo.	2	10	3	9	12	1	5
Group 3. Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)									
Living	13	13 mo.	3	9	6	4	5		2
Dead	7	6 mo.	1	5	3	2	2		2
Group 4. Patients treated for more than 1 year: two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal									
Living	30	12 mo.	6	23	22	7	5		3
Dead	10	17 mo.	1	7	5	3	5		
Total living	56		11	44	32	12	16		8
Total dead	109		9	52	21	55	48	2	40

The occurrence of congestive heart failure before the institution of treatment is of unfavorable prognostic import. In this series, it was less a feature in patients with aneurysm, only 27 per cent of whom suffered from decompensation or had previously suffered from congestive failure at the time of admission, than in those with aortic regurgitation, 46 per cent of whom were or had been so affected. Taking the group as a whole, 21 per cent of those still living had had heart failure before treatment, while it had occurred in 51 per cent of those now dead. Of 67 patients who had, or had had cardiac failure when treatment was

started, 12 are now living and 55 are dead, a mortality of 81 per cent. The average duration of life for the 12 survivors is 54 months; for the 55 who died, 24 months. Of the 96 who had not lost compensation before treatment, the corresponding figures are: living 44, average duration of life 69 months; dead 52, average duration of life 30 months; mortality 56 per cent. It appears, therefore, that the appearance of cardiac failure before treatment is started shortens life, on the average, by from 6 to 15 months. These data are shown in more detail for the various treatment groups in table 17. That congestive failure is not

TABLE 17.—*Relationship of Congestive Heart Failure to Outcome of Treatment in Patients with Cardiovascular Syphilis*

Treatment Group	Total Number of Patients in Subgroup	Number of Patients Living	Average Duration of Symptoms, Onset to Present	Number of Patients Dead	Average Duration of Symptoms, Onset to Death
Group 1. Patients with no treatment or very little					
Subgroup A*	41	1	66 mo.	40	23 mo.
Subgroup B†	36	6	68 mo.	30	26 mo.
Group 2. Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)					
Subgroup A	9	..	.....	9	17 mo.
Subgroup B	16	6	66 mo.	10	31 mo.
Group 3. Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)					
Subgroup A	7	5	53 mo.	2	27 mo.
Subgroup B	14	9	40 mo.	5	57 mo.
Group 4. Patients treated for more than 1 year: two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal					
Subgroup A	9	6	52 mo.	3	63 mo.
Subgroup B	30	23	81 mo.	7	31 mo.

* Patients in whom congestive heart failure was present before treatment.
† Patients in whom congestive heart failure was not present before treatment.

necessarily a barrier to a successful outcome of treatment is indicated by the fact that 12 of the surviving patients, 11 of whom were subsequently treated, had had decompensation before treatment was begun. In several of these patients, heart failure was extreme and recovery of compensation despaired of.

We attach less importance to the occurrence of attacks of congestive heart failure during or after treatment, though this was observed in only 33 per cent of those still living as contrasted with 69 per cent of those now dead (percentages calculated on total number of cases in which information was available). To some extent, at least, congestive heart failure occurring before treatment is started predisposes to subsequent similar attacks, as may be seen from the data of table 18. Here infor-

mation is provided as to the occurrence of cardiac failure during or after treatment in 46 patients who had experienced cardiac failure before treatment and in 70 who had not. The incidence of cardiac failure after treatment is 82 per cent in the former and only 40 per cent in the latter group. It is also apparent, however, that while congestive heart failure occurring during or after treatment is a serious complication, it need

TABLE 18.—*Relationship of Congestive Heart Failure Before Treatment to Heart Failure Occurring During or After Treatment*

Treatment Group	Total Number of Patients in Subgroup	Number Living	Number Who Had Cardiac Failure During or After Treatment	Number Who Did Not Have It	Number on Whom No Data as to This Was Obtained	Number Dead	Number Who Had Cardiac Failure During or After Treatment	Number Who Did Not Have It	Number on Whom No Data as to This Was Obtained
Group 1. Patients with no treatment or very little									
Subgroup A*	41	1			1	40	22	3	15
Subgroup B†	36	6	2	2	2	30	9	7	14
Group 2. Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)									
Subgroup A	9					9	6		3
Subgroup B	16	6	4	2		10	5	3	2
Group 3. Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)									
Subgroup A	7	5	5			2	2		
Subgroup B	14	9	1	6	2	5	1	1	3
Group 4. Patients treated for more than 1 year: two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal									
Subgroup A	9	6	1	4	1	3	2	1	
Subgroup B	30	23	4	17	2	7	2	4	1
Total									
Subgroup A	66	12	6	4	2	54	32	4	18
Subgroup B	96	44	11	27	6	52	17	15	20

* Patients in whom congestive heart failure was present before treatment.
† Patients in whom congestive heart failure was not present before treatment.

not prove to be more of a hindrance to a successful outcome than cardiac failure before treatment. Seventeen patients still living have had one or more attacks of heart failure since treatment was started, and six of these also had decompensation before any treatment was given.

In many instances, especially among Negro males, repeated attacks of cardiac failure occurred after treatment had started because of economic exigencies beyond our control or that of the patient. While we have made every effort to assist patients in obtaining light work, we

have not always been able to do so. The necessity of earning a bare living led many patients to return to former jobs even if they involved heavy physical labor. The cardiac reserve, estimated to be adequate to maintain the circulation during decreased activity, was unequal to the strain of stevedoring, hod-carrying, etc. Were we able to apply the ideal of restricted activity to all cases, the incidence of failure following the institution of treatment would be much lower. Indeed, considering the fact that our patients were drawn almost entirely from the laboring class, that the majority were Negroes, who are notoriously uncooperative

TABLE 19.—*Present Status of Living Patients Treated for Aneurysm and Aortic Regurgitation*

Treatment Group	Cardiovascular Condition	Number of Patients in Group Who Are Living	Number of These of Status Indicated		
			Have No Symptoms and Are Working	Have Persistent Symptoms but Are Able to Work	Have Persistent Symptoms and Are Incapacitated
Group 1. Patients with no treatment or very little	Aneurysm	2	..	1	1
	Aortic regurgitation	5	3	2	..
Group 2. Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	Aneurysm	2	..	..	2
	Aortic regurgitation	4	1	2	1
Group 3. Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	Aneurysm	3	2	1	..
	Aortic regurgitation	10	2	5	3
Group 4. Patients treated for more than 1 year; two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	Aneurysm	9	3	6	..
	Aortic regurgitation	21	10	9	2
Total		56	21	26	9

patients, and that treatment was carried out under the relatively inadequate conditions of an outpatient ambulant clinic, we feel that our results represent the minimum of benefit obtainable, rather than the possible maximum.

PRESENT STATUS OF LIVING PATIENTS WITH CARDIOVASCULAR SYPHILIS

Mere prolongation of life past the usual period of time would be of relatively small value to the patient if he remained completely incapacitated. It is therefore important to determine to what extent surviving patients are comfortable, free from incapacitating symptoms and able to work. Figures bearing on these points are presented in table 19. If

the group is taken as a whole, it will be seen that 21 of the 56 survivors are symptom-free and able to work. "Symptom-free," in these patients means almost exactly what it says. In most instances, of course, violent physical exercise results in a moderate amount of exertional dyspnea, but aside from this these patients are able to perform the ordinary tasks of their daily life without dyspnea, exertional or paroxysmal, and without pain or discomfort. Some of them, despite advice to the contrary, are still working at jobs involving heavy physical labor. Seven of these 21 patients are those who were symptom-free before treatment was started. The remaining 14, however, all had definite, sometimes incapacitating, symptoms before treatment. Included among the symptom-free group are 5 patients with aneurysm and 16 with aortic regurgitation.

Twenty-six patients, 9 with aneurysm and 17 with aortic regurgitation, are able to work regularly at some occupation involving little or no physical effort, such as preaching, boot-legging, etc., even though some symptoms persist. Most of these persons are distinctly better than before treatment was started, and the persisting symptoms are often very mild. It is important to note that 13 of the 21 symptom-free patients and 15 of the 26 who are able to work in spite of some remaining symptoms have been well treated (group 4) according to the scheme outlined in this paper.

Only 9 of the 56 surviving patients (3 with aneurysm and 6 with aortic insufficiency) are incapacitated and unable to do any work.

SYMPTOMATIC RELIEF FOLLOWING TREATMENT IN CARDIOVASCULAR SYPHILIS

Any one who has treated large numbers of patients with cardiovascular syphilis is struck by the prompt symptomatic relief that follows the improvement in the cardiac embarrassment and the institution of antisyphilitic treatment. It may be in part due, as Wile [30] insisted, to the general sense of well being that pervades any patient with late syphilis shortly after the institution of treatment, even though he may not have been feeling ill before. There is more than this, however; relief extends also to symptoms directly due to the cardiovascular lesion, especially paroxysmal and exertional dyspnea and pain. It is often so complete after a short time that the ignorant patient regards himself as cured, abandons further treatment and fails to return until the reappearance of distressing symptoms or a sudden cardiac break, occurring weeks or months later, forces him to seek relief anew. Without attempting the analysis of individual symptoms, details of which may be found in the paper by Hines and Carr,[34] we present the gross data as to symptomatic

34. Hines and Carr (footnote 28, fourth reference).

relief in table 20. We have excluded from consideration all patients who were symptom-free before treatment started, all those who received no treatment and those on whom adequate information was lacking. Included in treatment group 1 are patients who received, for example, as little treatment as one or two doses of arsphenamine, three or four injections of bismuth, or inunctions with mercury for a month or less. Even this infinitesimal amount of treatment brought about great symptomatic improvement in 3 of 11 patients with aneurysm and 6 of 20 with aortic regurgitation. It may easily be objected, and is perhaps true, that in these cases the relief was due not so much to antisyphilitic

TABLE 20.—*Symptomatic Relief from Antisyphilitic Treatment in Cardiovascular Syphilis*

Treatment Group	Patients with Aneurysm*			Patients with Aortic Regurgitation*		
	Total Number	Number Who Obtained Symptomatic Relief	Number Who Obtained No Relief	Total Number	Number Who Obtained Symptomatic Relief	Number Who Obtained No Relief
Group 1. Patients with no treatment or very little	11	3	8	26	6	20
Group 2. Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	7	4	3	13	2	11
Group 3. Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	5	4	1	12	10	2
Group 4. Patients treated for more than 1 year: two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	11	10	1	20	19	1
Total	34	21	13	71	37	33

* Excluding all who were not treated, those who were symptomless before treatment, and those in whom reliable data are lacking.

treatment as to the adjuvant medical measures of rest, digitalization, etc. It will be seen, however, that the probability of symptomatic relief is in direct proportion to the amount of treatment given. Of adequately treated patients (group 4), all except 1 of 11 patients with aneurysm and 1 of 20 with aortic regurgitation were markedly improved by treatment. While improvement is often dramatically prompt, as we have noted, it is sometimes discouragingly slow, and persistence and encouragement over a period of many months may be necessary. In some patients, discontinuance of antisyphilitic treatment is followed by a prompt recrudescence of symptoms, as illustrated by a patient with abdominal aneurysm who was free from pain as long as he was under treatment, but whose pain recurred after each lapse of a few weeks.

These data, as well as those given in table 19 as to the present status of living patients, constitute as forceful an argument for the adequate antisyphilitic treatment of cardiovascular syphilis as do the figures given for prolongation of life.

ALTERATION OF PHYSICAL SIGNS BY TREATMENT

Stokes [35] and Brooks,[29] among other writers, emphasized not only symptomatic improvement resulting from treatment, but also improvement or alteration in physical signs. In apparently uncomplicated aortitis, for example, the institution of treatment may be shortly followed by the appearance of a diastolic murmur, not previously heard; an aneurysmal sac may pulsate more widely after than before treatment, owing to the resolution of the inflammatory tissue in syphilitic mediastinitis or peri-aortitis; a faint diastolic murmur may become much louder. This paradoxical increase in physical signs is not so bad as it seems. As Stokes put it, "The patient has exchanged a progressive disability for an arrested and static one." These phenomena are sometimes of great value as a therapeutic test in suspected but Wassermann-negative cardiovascular syphilis. On the other hand, cardiac murmurs may completely disappear, aortic widening as measured by teleroentgenography may decrease, and rarely a definite sacculation of the aorta may vanish. Stokes [36] reported one such "disappearing aneurysm," and we have seen another, which will be separately reported.[37] We have made no attempt at tabulation of changes in physical signs during or after treatment in our material, though we agree with Stokes and Brooks that such changes infrequently occur.

INFLUENCE OF TREATMENT IN CARDIOVASCULAR SYPHILIS ON ABILITY TO WORK

The question of the utility of treatment may be approached from still another angle, namely, ability to work before and after treatment. This information is gathered in table 21. The figures speak for themselves. Let us compare the percentage probability of various outcomes in inadequately treated (groups 1 and 2) as compared with relatively adequately treated (groups 3 and 4) patients. Of 69 patients in groups 1 and 2, 62 per cent were unable to work either before or after the institution of treatment; 21 per cent were unable to work before, but could work afterward; 8 per cent, able to work before, were unable afterward, and 6 per cent were able to work both before and after treatment. Con-

35. Stokes (footnote 17, p. 832).

36. Stokes (footnote 17, p. 886).

37. Moore, J. E.; Danglade, J. H., and Reisinger, J. C.: Diagnosis of Syphilitic Aortitis Uncomplicated by Aortic Regurgitation or Aneurysm: Comparison of Clinical and Necropsy Observations in One Hundred and Five Patients, Arch. Int. Med. **49**:752 (May) 1932.

trast this with the corresponding figures for the 49 patients in groups 3 and 4. Only 16 per cent were unable to work before or after treatment; 39 per cent were so improved by treatment that, unable to work before, they could work afterward; none of those able to work before grew so much worse under treatment as to be unable to work afterward, while 44 per cent, able to work before, were maintained in a sufficiently good state of health as to be able to continue afterward.

TABLE 21.—*Influence of Treatment on Ability to Work in Cardiovascular Syphilis (Aneurysm and Aortic Regurgitation)*

Treatment Group	Number of Patients with Data Available	Number Unable to Work Before or After Treatment	Number Unable to Work Before, but Able After Treatment	Number Able to Work Before, but Unable After Treatment	Number Able to Work Before and After Treatment
Group 1. Patients with no treatment or very little	52	37	8	5	2
Group 2. Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	17	6	7	1	3
Group 3. Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	16	3	7	...	6
Group 4. Patients treated for more than 1 year: two courses of an arsenical drug and two of a heavy metal, or four courses of a heavy metal	33	5	12	...	16

TABLE 22.—*Average Period of Incapacity After Varying Amounts of Treatment in Cardiovascular Syphilis (Aneurysm and Aortic Regurgitation)*

Treatment Group	Number of Patients with Data Available	Number Never Incapacitated Until Final Illness or Last Observation	Average Period of Incapacity
Group 1. Patients with no treatment or very little	46	2	15 mo.
Group 2. Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	15	2	14 mo.
Group 3. Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months	19	6	9 mo.
Group 4. Patients treated for more than 1 year: two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	35	16	10 mo.

AVERAGE PERIOD OF INCAPACITY AFTER VARYING AMOUNTS OF TREATMENT IN CARDIOVASCULAR SYPHILIS

It may seem like piling Ossa on Pelion to adduce still further evidence that the antisyphilitic treatment for cardiovascular syphilis is of value. The prevailing skepticism of many physicians makes it of the utmost importance to consider the question from all possible angles. In table

22, we present data relative to the total period of incapacity of the patients in our various treatment groups. Comparing again untreated or inadequately treated patients (groups 1 and 2) with those receiving relatively adequate treatment (groups 3 and 4), we point out that only 6 per cent of the 61 patients of the former, as compared with 40 per cent of the 54 patients of the latter, classification, were never incapacitated until the date of the last observation or the onset of the final illness. This is, of course, a direct reflection of the incidence of congestive heart failure before and after treatment, a factor already analyzed in tables 16, 17 and 18. The average period of incapacity for the patients of groups 1 and 2 was between fourteen and fifteen months; that for the patients of groups 3 and 4 was between nine and ten months. When

TABLE 23.—*Cause of Death in Aneurysm*

Treatment Group	Number Dead	Number Who Died of Cardiovascular Syphilis		Number Who Died, Cause Unknown	Number Who Died from Other Cause
		Death Probably or Certainly Gradual	Sudden Death		
Group 1. Patients with no treatment or very little	20	8	8	3	1 (pulmonary tuberculosis)
Group 2. Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal from (1½ to 4 months)	8	3	1	2	2 (1 pulmonary tuberculosis, 1 chronic nephritis)
Group 3. Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	3	3	..	..	..
Group 4. Patients treated for more than 1 year; two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	6	3	1	..	2 (1 miliary tuberculosis, 1 carcinoma)
Total	37	17	10	5	5

one considers that the well treated patients have been under observation for periods of time averaging from twice to three times as long as those untreated or poorly treated, these figures take on added significance.

CAUSE OF DEATH IN TREATED PATIENTS WITH ANEURYSM AND AORTIC REGURGITATION

Our information concerning the causes of death in the patients of this series was gathered from personal observation of patients who died while under our supervision, from the records of other hospitals, from the data given on death certificates signed by outside physicians, and from descriptions of patients' last illnesses supplied by relatives or by friends. The inclusion of the last two sources of information, and the absence of a necropsy in most instances, introduce an unavoidable inaccuracy into our statements. However, we present the data for what they

re worth in tables 23 and 24. Fifty-seven patients, of whom 17 had aortic aneurysm and 40 aortic regurgitation, died from progressive cardiac failure, presumably due, of course, to cardiovascular syphilis. Ten patients with aneurysm, or 27 per cent of those dead, and 18 with aortic regurgitation, or 25 per cent of those dead, died suddenly; that is, the patients, previously in their usual state of health, dropped dead or were found dead in bed. Rupture of the aneurysm was the usual cause of sudden death in the patients with this condition. The precise cause of

TABLE 24.—*Cause of Death in Aortic Regurgitation*

Treatment Group	Number Dead	Number Who Died of Cardiovascular Syphilis		Number Who Died, Cause Unknown	Number Who Died from Other Cause
		Death Probably or Certainly Gradual	Sudden Death		
Group 1. Patients with no treatment or very little	52	29	13	5	5 (1 chronic nephritis, 1 carcinoma, 1 acute nephritis, 1 pulmonary tuberculosis, 1 tuberculous meningitis)
Group 2. Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	12	8	2	1	1 (pulmonary tuberculosis)
Group 3. Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	4	2	1	..	1 (sarcoma)
Group 4. Patients treated for more than 1 year: two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	4	1	2	..	1 (lobar pnuemonia)
Total.....	72	40	18	6	8

sudden death in patients with aortic regurgitation is not clear, in spite of numerous pathologic studies by Warthin,[38] Martland[39] and others; it is certainly not always, nor apparently even often, due to sudden coronary occlusion, and it is difficult to be satisfied with Warthin's explanation that it is due to cardiac insufficiency and dilatation resulting from diffuse interstitial myocarditis of slight degree, leading eventually to fibrosis.

38. Warthin, A. S.: The Role of Syphilis in the Etiology of Angina Pectoris, Coronary Arteriosclerosis and Thrombosis, and of Sudden Cardiac Death, Am. Heart J. **6**:163, 1930.

39. Martland, H. S.: Syphilis of the Aorta and Heart, Am. Heart J. **6**:1, 1930.

Eleven patients were reported by relatives or by friends to have died, but the information supplied was too meager for us to assign any definite cause. Presumably most of them died from cardiovascular syphilis.

Thirteen patients, 5 with aneurysm and 8 with aortic regurgitation, died from illnesses unrelated to cardiovascular syphilis. The causes of death are given in the tables. Four of these patients (the two with aneurysm who died of carcinoma and miliary tuberculosis, respectively, and the two with aortic regurgitation who died of sarcoma and lobar pneumonia, respectively, in each instance after adequate treatment for syphilis) were doing exceptionally well from the standpoint of cardiovascular syphilis at the time of death.

USE OF ARSENICAL DRUGS IN CARDIOVASCULAR SYPHILIS

We have repeatedly stressed in this paper and elsewhere that one aim of treatment in cardiovascular syphilis is the absolute avoidance of

TABLE 25.—*Use of Arsenical Drugs in Cardiovascular Syphilis (Aneurysm and Aortic Regurgitation)*

Type of Arsenical Drug Administered	Number of Patients Receiving Drug*	Number Who Gave Serious Reactions
Neoarsphenamine	60	3
Arsphenamine	30	4
Silver arsphenamine	14	0
Tryparsamide	14	1
Sulpharsphenamine	1	0
Bismarsen	1	0

* The total number of patients treated with some arsenical product was 92; the total number of patients receiving bismuth or mercury (and potassium iodide) was only 50.

reactions to treatment. Even such otherwise unimportant reactions as slight nausea and vomiting throw an undue strain on an overburdened heart which must be eliminated if possible. Therapeutic shock (the Jarisch-Herxheimer reaction) and the therapeutic paradox are irremediable disasters. The loss of many of our older records (prior to 1920) through the inadequate system of cross-indexing prevalent at the time prevents us from including here a report on the frequency of sudden death following the use of average therapeutic doses of old arsphenamine. We have observed at least four instances of such deaths, not included in this series.

We have thought it profitable, however, to inquire into the various arsenical drugs given our patients and the incidence of serious or alarming reactions following their use. This information is summarized in table 25. Twenty-three of the 165 patients in this series received no treatment of any kind and are eliminated from consideration in the table. Fifty were treated exclusively with a heavy metal (bismuth or mercury)

and the iodides. This is a reflection of two factors, first, that in many patients with preceding heart failure and a low cardiac reserve the use of arsenical drugs was thought to be contraindicated; second, that many patients were so much improved symptomatically after a single course of a heavy metal that they failed to return for further treatment.

Ninety-two patients were treated with one or more of the arsenical drugs listed. The majority received neoarsphenamine in small dosage (from 0.1 to 0.45 Gm., rarely more than 0.3 Gm.). In 3 of 60 patients so treated, the use of this drug was followed by reactions severe enough to preclude its further employment. A shower of ventricular extrasystoles was precipitated by each injection in one patient; while, in the other two, each attempt at this type of treatment was followed by fever, nausea and vomiting and extreme malaise lasting over a period of several days. There were no instances of sudden death following the use of neoarsphenamine.

Thirty patients received old arsphenamine (606) in a dosage usually not exceeding 0.1 Gm. Of these, 2 died suddenly within twenty-four hours following a treatment. In one, death resulted from circulatory collapse on the treatment table, probably to be ascribed to ventricular fibrillation resulting from the direct toxic action of the drug on a damaged myocardium; in one, sudden death resulted from a ruptured aneurysm about eighteen hours after the first injection of the drug, which in this case had not been preceded by any preparatory treatment. This death was almost certainly a Jarisch-Herxheimer effect—therapeutic shock. In another patient, circulatory collapse occurred on the table during treatment, but the patient recovered after forty-eight anxious hours. The fourth serious reaction occurred in one of the patients who reacted badly after neoarsphenamine, and was identical with the after-effects of that drug.

In 14 patients treated with silver arsphenamine, 1 with sulpharsphenamine and 1 with bismarsen, there were no serious reactions. The number of patients given silver arsphenamine is too small for us to express an opinion as to its therapeutic efficacy. We have the impression that it may be profitable to attempt its use in small doses (from 0.05 to 0.1 Gm.) in patients in whom mild reactions developed after the use of neoarsphenamine, and that it may be equally efficacious from the therapeutic standpoint. Sulpharsphenamine has been dropped from our therapeutic armamentarium not because of any special deleterious effect in cardiovascular syphilis, but because of the generally high incidence of dermatitis and blood dyscrasias following its use. We are employing bismarsen with increasing frequency in cardiovascular syphilis, but none of the patients treated with it have as yet been followed long enough to justify their inclusion in this series.

Tryparsamide has been employed in 14 patients, practically all of whom had complicating neurosyphilis. One patient died of a ruptured aneurysm twenty-four hours after the first dose (probable therapeutic shock). Aside from this case, the use of tryparsamide in average therapeutic dosage (3 Gm.) was not attended by any deleterious after-effect on the cardiovascular apparatus. On the other hand, we have seen nothing to indicate that it has any therapeutic value in cardiovascular syphilis, and believe that its use should be limited to those patients in whom involvement of the central nervous system is a complicating feature. Even here it should not be employed until thorough preparatory treatment has been given.

Our experience demonstrates, we think, that therapeutic shock can be almost entirely eliminated as an important factor in the treatment of patients with cardiovascular syphilis by long and thorough preparatory treatment with bismuth or mercury and the iodides, and by an appropriate small dosage of the arsphenamine employed. The arsenical product of choice in our experience is neoarsphenamine, with bismarsen second and silver arsphenamine third. Old arsphenamine should never be used in any dosage in a patient with cardiovascular syphilis (except uncomplicated aortitis, of which more will be said in a subsequent communication).

We can offer no statistical information as to the incidence of the therapeutic paradox. In 66 patients, congestive heart failure developed after treatment had begun, but the factors leading to this difficulty are so numerous and complex as to defy further analysis than we have already attempted. Individual cases might be cited to show that the therapeutic paradox is an important consideration. It can be largely avoided, we think, only by proper attention to adequate preparatory treatment, a correct estimate of the cardiac reserve, clinical acumen in selecting the proper time, drug and dosage for arsenical treatment, and the intelligent use of digitalis, rest and restriction of activity.

EFFECT OF ANTISYPHILITIC TREATMENT ON THE WASSERMANN REACTION OF THE BLOOD IN CARDIOVASCULAR SYPHILIS

The least important effect of treatment in cardiovascular syphilis is that on the Wassermann reaction of the blood. As has been repeatedly pointed out, patients with this type of syphilitic lesion are prone to have a persistently positive Wassermann reaction of the blood in spite of treatment. Information on this point is summarized in table 26. The important point is that 57 per cent of the 33 patients in treatment group 4 had a fixed positive Wassermann reaction after a great deal of treatment. We feel that, for all practical purposes, the response of this reaction of the blood to treatment may be completely disregarded

in cardiovascular syphilis. It is most unwise to base the discontinuance of treatment on the condition of obtaining a negative Wassermann reaction. This may never be accomplished, on the one hand, and on the other, if treatment is stopped when the reaction becomes negative or remains so for any arbitrary period of time, the patient may be deprived of the treatment which he needs to keep his lesion quiescent. Clinical and pathologic progression may and often does occur in the presence of a negative Wassermann reaction of the blood. It is important to reassure the patient of the relative lack of significance of a persistently positive reaction, since otherwise he may become discouraged by what seems to him the apparent inefficacy of the treatment.

The aim of treatment in cardiovascular syphilis is to maintain the patient in relatively good health over as long a period of time as possible. Radical cure of the syphilitic infection is of course out of the question.

TABLE 26.—*Effect of Antisyphilitic Treatment on the Wassermann Reaction of the Blood in Patients with Cardiovascular Syphilis (Aneurysm and Aortic Regurgitation)*

Treatment Group	Total Number of Patients	Number the Wassermann Reaction of Whose Blood		
		Remained Positive	Was Reduced	Was Reversed
Group 2. Patients with equivalent of one course of an arsenical drug or one long course of a heavy metal (from 1½ to 4 months)	19	12	2	5
Group 3. Patients with equivalent of one long course each of an arsenical drug and of a heavy metal (from 4 to 12 months)	19	15	1	3
Group 4. Patients treated for more than 1 year: two courses of an arsenical drug and two of a heavy metal, or four of a heavy metal	33	19	..	14

SUMMARY AND CONCLUSIONS

1. We present a general consideration of the subject of the treatment of cardiovascular syphilis, based on 53 patients with aortic aneurysm and 112 with aortic regurgitation. At the same time, our material permits some conclusions bearing on important questions of the incidence of cardiovascular syphilis.

2. An earlier study of the outcome of treatment in early syphilis in our clinic revealed that cardiovascular syphilis developed among these treated patients in inverse ratio to the amount of treatment given early in the infection. Not one of 117 patients with early syphilis who received three or more courses of arsphenamine, and treatment with mercury during periods between the courses, presented any evidence of cardiovascular involvement during the period of observation, while 24 of

285 patients who had received less than this amount of treatment were observed to acquire syphilitic aortitis, aneurysm or aortic regurgitation. Adequate treatment for early syphilis almost certainly protects the majority of patients so treated against subsequent cardiovascular syphilis.

3. Of 6,420 patients from our own clinic with various forms of late syphilis, 10 per cent had cardiovascular syphilis. Of the total number, 2.7 per cent had aortic regurgitation and 1.2 per cent aortic aneurysm. These were the clinical diagnoses on admission to the hospital.

4. Cardiovascular syphilis is twice as common in males as in females and about twice as common in Negro as in white patients.

5. Pathologic studies carried out by various investigators indicate that from 70 to 90 per cent of all patients with late syphilis show postmortem evidence of syphilis of the aorta.

6. The majority of cases of aneurysm and aortic regurgitation occur in the fifth decade of life. White patients appear to be affected later in life than Negroes, and males later than females.

7. About one half of all patients with cardiovascular syphilis can give no history of infection with syphilis. Symptomless infection must be a fairly frequent occurrence. The average interval of time between infection and the development of cardiovascular symptoms is about twenty years.

8. In 20 of our 165 patients, the aneurysm or the aortic regurgitation had caused no symptoms, and was accidentally discovered during routine physical examination. The onset of symptoms was usually abrupt, but sometimes was slow and insidious.

9. All except 13 of the 165 patients in this series had been subjected to the strain of hard physical labor.

10. The most frequent association with other lesions of syphilis was that with syphilis of the central nervous system (especially tabes dorsalis), which occurred in from 17 to 18 per cent of our patients.

11. An additional 17 per cent of patients with cardiovascular syphilis, but without clinical evidence of neurosyphilis, had abnormal spinal fluids. The actual incidence of complicating neurosyphilis was thus about 35 per cent.

12. Positive Wassermann reactions of the blood were obtained for 98 per cent of our patients with aneurysm, and 96 per cent of those with aortic regurgitation.

13. The association of cardiovascular syphilis and neurosyphilis as a complicating factor in treatment is discussed.

14. One hundred and forty-seven (89 per cent) of our patients had never received any treatment for syphilis before the development of cardiovascular syphilis. Of the remainder, not one had received ade-

quate treatment for early syphilis. Only 4 of the 165 had received arsphenamine at the time of early syphilis, and none of these got more than three injections.

15. These data, with those given in the second paragraph of this summary, constitute a powerful argument for the adequate treatment of early syphilis. They also indicate that modern antisyphilitic treatment is probably not responsible for the apparent increase in the incidence of syphilitic aortitis.

16. The literature on the treatment of cardiovascular syphilis is briefly reviewed.

17. The evolution of the method of treatment now in use by us and, subject to minor modifications, by many other investigators, is outlined. Especially stress is laid on sudden death during or immediately following the administration of arsphenamine to patients with syphilitic heart disease, presumably due to ventricular fibrillation; on sudden death from twenty-four to forty-eight hours following an injection, due to therapeutic shock (the Jarisch-Herxheimer reaction), and on the therapeutic paradox.

18. The measures taken to avoid these reactions have resulted in the adoption of a method of treatment which is described in detail. This method includes adequate general medical care and the cautious use of mercury, bismuth, the iodides, neoarsphenamine and bismarsen in small doses. All reactions to treatment are meticulously avoided, and treatment is prolonged over a period of years.

19. Using this method of treatment and subdividing our material into four groups, on the basis of the amount of treatment given, we have shown that in 22 patients with aortic aneurysm, who received little or no treatment, the mortality during the period of observation was 90 per cent, and that the average duration of life from the onset of symptoms to deaths or, in living patients, to the last observation, was 19 months. In 15 well treated patients with aortic aneurysm, the mortality was 40 per cent, and the average duration of life 75 months.

20. The mortality in 57 patients with aortic regurgitation who received little or no treatment was 91 per cent, and the average duration of life 30 months. In 25 well treated patients, the mortality was 16 per cent, and the average duration of life 71 months.

21. It is mathematically demonstrable that these data are probably statistically significant.

22. So far as can be judged from the average duration of symptoms, the respective numbers of patients symptom-free before and after treatment, and the incidence of congestive heart failure before and after treatment in the various treatment groups, the patients in the

various groups were approximately similar. That is, it does not appear that our reported deaths occurred only among patients desperately ill before treatment, and our reported success only among patients with less serious or less rapidly progressive lesions.

23. The occurrence of congestive heart failure before or after treatment is of serious prognostic import. In this connection, we present analyses of our material from several standpoints.

24. Twenty-one of the surviving 56 patients of this series are symptom-free and able to work; 26 have some persistent symptoms, but can carry on at light work; 9 are incapacitated. Twenty-eight of the 47 still able to work were well treated for syphilis.

25. Symptomatic relief in cardiovascular syphilis is frequently obtained, and its probability is in direct proportion to the amount of treatment given.

26. The occasional alteration of physical signs during or after treatment is discussed.

27. In an analysis from the standpoint of ability to work before and after treatment, well treated patients show up much more favorably than those untreated or badly treated.

28. Complete incapacity is much less frequent and of shorter duration in well treated than in poorly treated patients.

29. Fifty-seven of our 165 patients died of progressive cardiac failure; 28 (10 with aneurysm and 18 with aortic regurgitation) died suddenly; 11 are dead, but the cause of death is unknown; 13 died of some cause other than cardiovascular syphilis.

30. The arsenical drugs given to our patients are tabulated and the reactions to them analyzed. From these data we conclude that the arsenical drugs of choice are, in order, neoarsphenamine, bismarsen and silver arsphenamine. Old arsphenamine (606) should not be employed in patients with aneurysm or aortic regurgitation. The use of tryparsamide should be limited to patients with complicating neurosyphilis.

31. A fixed positive Wassermann reaction of the blood is the rule in cardiovascular syphilis, and the response of this reaction to treatment may be completely disregarded.

32. From the analysis of our material, we conclude that properly supervised antisyphilitic treatment, with adequate general medical care, given to patients with aneurysm or aortic regurgitation, prolongs life, alleviates symptoms, maintains the ability to pursue a gainful occupation and reduces the period of incapacity.

A POSSIBLE RELATIONSHIP OF PANCREATIC INSUFFICIENCY TO ADDISON-BIERMER (PERNICIOUS) ANEMIA

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As a result of the investigations of Whipple, Minot, Castle and others, the present conception of Addison-Biermer anemia is that it is a deficiency disease of a distinct type. An insufficient amount of some protein derivative is available for normal red blood corpuscle maturation, finally resulting in megaloblastic, macrocytic, hyperchromic anemia and hyperbilirubinemia. This lack of necessary protein derivative may be dependent in part on an inadequate intake of readily available protein, such as that contained in liver and stomach, and in part on inadequate digestion of less available protein-containing substances, such as beef. It has been contended by Castle and his co-workers [1] that the lack of normal protein digestion resulting in anemia is in some way due to the gastric achylia, although Castle has been unable to show what the necessary missing factor is. He has shown by feeding experiments that it is not hydrochloric acid and not pepsin, that it is present in the gastric contents of patients without pernicious anemia, and that it has the properties of an enzyme. He has designated it as an unknown intrinsic factor. He felt that it was not contained in duodenal contents regurgitated into the stomach.

In 1929, Landau and Glass [2] reported a large series of miscellaneous cases in which they analyzed the fasting gastric contents and also the duodenal contents for pancreatic enzymes. Only nine of the whole series showed what the authors termed both gastric and pancreatic achylia. Eight of these were definite cases of Addison-Biermer anemia. Six of the eight had no trypsin at all, and the other two showed the extremely low amount of only *2* units. The ninth case was insufficiently studied to permit a diagnosis. More recently, Kunos and Gerö [3] have

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1. Castle, W. B.; Townsend, W. C., and Heath, C. W.: Am. J. M. Sc. **180**: 305, 1930.
2. Landau, A., and Glass, J.: Arch. f. Verdauungskr. **46**:192, 1929.
3. Kunos, I., and Gerö, S.: Gyógyászat **70**:344, 1930.

noted similar findings. As the fasting gastric content contains approximately the same concentration of pancreatic enzymes as the fasting duodenal content, except in hyperchlorhydria, we examined the fasting gastric contents of ten untreated patients with Addison-Biermer anemia for trypsin, and found it absent in nine. In the tenth case there was only 2.5 units. In sixty other cases, mostly with achlorhydria, trypsin was present in the contents of the fasting stomach in normal amounts. Although such a lack of trypsin secretion in cases of Addison-Biermer anemia is contrary to the findings in the two cases reported by McClure [4] in 1922, it seems sufficiently striking to suggest a relationship to the inadequate protein digestion occurring in Addison-Biermer anemia.

Such a relationship is also suggested by the red blood macrocytosis occurring in diseases of the pancreas.[5] The only conditions without marked anemia in which such a macrocytosis is found are the primary anemias, certain cases of jaundice and pancreatic disorders. In nine cases of cancer of the pancreas, all showed an erythrocyte macrocytosis ranging from 7.9 to 8.5 microns. In each of these cases our diagnosis was proved by operation or by autopsy. Landau and Glass [2] discussed cases both of definite pancreatic disease and of primary anemia.

If the secretion of trypsin is necessary for the normal digestion of proteins, and if its absence, which is rare, is associated with a primary type of anemia, it seems possible that its enzymic action is essential to the prevention of Addison-Biermer anemia. Trypsin might be the unknown intrinsic factor of Castle, not secreted by the stomach, but present owing to regurgitation from the duodenum. Normal human gastric juice, even though free from bile, contains trypsin, except when the stomach is emptying rapidly.[6] In order to test such a hypothesis it was decided to duplicate Castle's feeding experiments with digested beef, but to use preparations of trypsin in solution to digest the meat instead of human gastric juice.

EXPERIMENTAL DATA

In each experiment we carried out, the trypsin-containing solution was made up to 300 cc. by the addition of distilled water, and incubated for two hours at 37 C. with 200 Gm. of fat-free beef ground up as hamburger steak. The resultant filtrate was passed through gauze and given the patient to drink, warm or cold. No difficulty was encountered in administering the digested beef solution to the patients, except in one case of an old woman. Feedings were carried out over periods varying from seven to twenty-three days. Each patient, with one exception

4. McClure, C. W., and Jones, C. M.: Boston M. & S. J. **187**:909, 1922.

5. von Boros, J.: Wien. Arch. f. inn. Med. **12**:243, 1926.

6. Martin, Lay: Biliary, Pancreatic and Duodenal Studies: Estimation of the Pancreatic Enzymes and Value of Such Determinations from a Clinical Standpoint, Arch. Int. Med. **39**:343 (March) 1927.

to be noted later, had a definite case of Addison-Biermer anemia, and responded in the usual way to adequate amounts of liver extract.

Experiments in the Digestion of Beef by Solutions Containing Trypsin.—As none of the experiments gave any positive results, they will be described only briefly. Pancreatin (Armour) was used as a beef digestant in three different cases without any effect on the red cell count, the hemoglobin determinations, the production of reticulocytes or the size of the cells as determined by the halometer.[7] Each patient was fed for fourteen successive days. Bile with high trypsin content obtained from a human biliary fistula was used daily as a digestant for two weeks without effect, and pancreatic juice from the pancreatic fistula of a dog was equally ineffective over a seven day period. Dr. Nelson Howard performed the operation on the dog. A solution of powdered trypsin (Armour), with a strength of about 100 units (Gross) of enzyme activity, also failed to produce effective digestion of the beef.

These results demonstrated that a solution of trypsin alone was ineffective in the digestion of beef; so it was decided to try a solution more nearly simulating normal human gastric contents. As we wished to obtain protein digestion similar to that occurring physiologically, we employed both the proteolytic enzymes commonly found in the stomach contents.

Experiments in the Digestion of Beef by Solutions of Trypsin, Pepsin and Hydrochloric Acid.—A solution of enzymes was made up which might be termed artificial gastric contents as far as protein digestion was involved. This consisted of 300 cc. of distilled water to which approximately 1 Gm. of powdered trypsin, 2 Gm. of powdered pepsin (Armour) and from 2.5 to 3 cc. of concentrated hydrochloric acid were added. This furnished a trypsin concentration of about 100 units, an adequate amount of pepsin in terms of Castle's similar work and a free acidity of from 90 to 100 degrees. The solution was thoroughly mixed by stirring; 200 Gm. of ground beef was added, and incubation was carried out as in the previous experiments. The filtrate obtained was fed to two patients with Addison-Biermer anemia and to one patient with sprue with a blood picture of pernicious anemia. Four feeding experiments were carried out on the three patients, and a typical response to liver therapy was demonstrated in each during the stay in the hospital.

Case 1.—An old woman with arteriosclerosis, who was suffering from senile mental changes and diarrhea, had been failing clinically for one month before experiment 1 was started. She showed glossitis, hyperbilirubinemia with a negative direct van den Bergh reaction, absence of trypsin in the gastric contents during fasting and in the duodenal contents, and achlorhydria following the injection of histamine. The blood findings before, during and after treatment are shown in table 1. The first experiment consisted of eight consecutive feedings, and was then stopped so that the patient might be utilized for a second experiment. During the feedings she gained 9 per cent of hemoglobin and 590,000 red blood corpuscles in six days, the gain ceasing coincident with the cessation of therapy. The reticulocytes rose to 5 per cent on the seventh day, and the corresponding typical alteration in cell size[8] developed its maximum on the seventh day. The blood count then

7. Cheney, G.: California & West. Med. **34**:40, 1931.
8. Fitzhugh, G., and Persons, E. L.: J. Clin. Investigation **7**:631, 1927.

remained practically stationary, the reticulocyte count returned to normal, and the average diameter of the erythrocytes returned to the original figure. After six days experiment 2 was started, and the patient was again fed, this time for a period of twenty-three days. During this experiment, the red cell and reticulocyte response were typical of that produced by the administration of slightly inadequate amounts of liver, as described by Minot and his co-workers,[9] in that the erythrocyte count improved only a little, and there was a much prolonged but not intense response of the reticulated red cells. No improvement occurred after the cessation of therapy, and the reticulocyte count fell. The changes in red cell size were again comparable to those in the reticulocyte figures in this experiment.

TABLE 1.—*Results of Experiments 1 and 2 on the Blood Picture in a Case of Addison-Biermer Anemia and Pronounced Arteriosclerosis*

	Red Blood Cells	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Diameter, Microns
Before 1st feeding				
27th day	2,100,000	40	...	8.0
9th day	1,520,000	36	...	8.0
3d day	1,230,000	34	...	8.0
During 1st feeding				
1st day	1,200,000	32	0.4	8.0
3d day	1,230,000	34	...	7.8
5th day	1,550,000	40	0.9	7.8
7th day	1,790,000	40	5.0	7.6
Before 2d feeding				
7th day	1,760,000	41	3.1	7.7
4th day	1,780,000	40	3.0	7.9
2d day	1,700,000	40	0.1	8.0
During 2d feeding				
1st day	1,760,000	40	0.1	8.0
4th day	1,700,000	40	1.6	7.8
6th day	1,700,000	40	4.0	7.6
8th day	1,600,000	40	3.6	7.7
9th day	.....	...	3.7	7.7
11th day	1,500,000	40	4.0	7.6
12th day	1,500,000	40	5.0	7.7
13th day	.....	...	5.1	7.8
14th day	1,570,000	40	5.8	7.8
18th day	2,170,000	45	5.0	7.9
20th day	2,050,000	45	5.0	8.0
23d day	1,800,000	43	4.0	8.0
After 2d feeding				
3d day	2,000,000	45	4.0	8.0
6th day	1,750,000	43	3.0	8.0

CASE 2.—Experiment 3 was similarly carried out in a man 56 years old. The blood findings are shown in table 2. The icteric index was 14 units. The direct van den Bergh reaction was negative. The fasting gastric contents contained no trypsin. Gastric analysis after the injection of histamine failed to reveal any free acidity. A bone marrow puncture showed a typical picture of pernicious anemia. The Price-Jones curve was also typical. The blood count was stationary for nine days before the special therapy was instituted, which was continued for eleven days. There was a gain of approximately 1,000,000 red blood corpuscles and 20 per cent hemoglobin coincident with the special feedings. No reticulocyte response occurred, but the average diameter of the erythrocytes showed the characteristic changes, the smallest occurring on the eighth day.

9. Minot, G. R.; Cohn, E. J.; Murphy, W. P., and Lawson, H. A.: Am. J. M. Sc. **175**:599, 1928. Minot, G. R.; Murphy, W. P., and Stetson, R. P.: ibid., p. 581.

Case 3.—Experiment 4 was carried out on a German woman aged 60, who for three years, since living in Shanghai, had had recurrent attacks of glossitis, weakness with anemia and diarrhea with large, bulky stools. The blood showed macrocytic hyperchromic anemia with leukopenia identical with that found in Addison-Biermer anemia, and a bone marrow puncture showed an identical picture. There were 50 units of trypsin present in each of two samples of gastric contents obtained during fasting, and free acidity was found on three gastric analyses. The stools were characteristic of sprue. The blood findings before, during and after treatment are recorded in table 3. It is noteworthy that the blood count was practically stationary for three weeks before the experiment was started.

Table 2.—*Results of Experiment 3 on the Blood Picture in a Case of Addison-Biermer Anemia*

	Red Blood Cells	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Diameter, Microns
Before feeding				
9th day	2,720,000	62	0.5	7.7
2d day	2,820,000	60	0.5	7.7
During feeding				
2d day	2,980,000	68	3.5	7.7
6th day	3,500,000	75	0.5	7.5
8th day	3,600,000	75	0.5	7.1
10th day	3,850,000	78	0.5	7.5
After feeding				
1st day	3,910,000	80	...	7.4
4th day	4,080,000	82	...	7.5

Table 3.—*Results of Experiment 4 on the Blood Picture in a Case of Sprue with a Typical Primary Type of Anemia*

	Red Blood Cells	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Diameter, Microns
Before feeding				
22d day	1,500,000	47	...	...
20th day	1,550,000	45	...	8.8
9th day	1,500,000	48	...	8.7
During feeding				
1st day	1,420,000	48	>0.5	8.6
5th day	1,400,000	50	4.0	8.6
8th day	1,380,000	50	3.0	8.3
12th day	1,800,000	52	1.0	8.4
15th day	2,032,000	57	0.5	8.5
After feeding				
3d day	2,238,000	58	>0.5	8.4
6th day	2,190,000	60	0.5	8.4
11th day	2,160,000	62	0.5	8.4
14th day	2,140,000	62	0.5	8.4

As it has been shown that this type of sprue with anemia responds to treatment with liver extract in the same manner as does pernicious anemia,[10] it was thought that if a sufficient amount of red blood corpuscle maturation factor could be produced by digesting beef, a similar response might be obtained. As both free hydrochloric acid and trypsin were present in this patient, the object was to introduce a larger amount of the necessary protein derivative than she could herself digest and absorb. She was fed for fifteen days in the same manner as the patients in cases 1 and 2. The hemoglobin rose 10 per cent, and the red blood count increased

10. West, Randolph: Porto Rico Rev. Pub. Health **3-4**:219, 1927-1929.

800,000 cells by the second day after feeding was discontinued, and then remained approximately stationary for two weeks. The red blood count did not start to increase until after the ninth day of therapy, and gained on an average of 100,000 cells a day for eight consecutive days. The reticulocyte count rose to 4 per cent on the sixth day and gradually fell to less than 0.5 per cent on the fourteenth day. The average red cell diameter also diminished in the characteristic manner, reaching the lowest point on the ninth day.

Two further experiments were carried out in order to determine if only small amounts of trypsin would produce the same results as in the four preceding feeding tests. The solution was made up in the same way, containing the same amounts of water, pepsin and hydrochloric acid, but only enough trypsin was added to give a concentration of between 2.5 and 5 units. Such trypsin values are below the low limits of normal, and occur but rarely. This artificial gastric content, inadequate in trypsin, was used to digest the beef, and the resultant filtrate was fed to two patients with Addison-Biermer anemia. In the first case the feedings were continued for twelve consecutive days, and in the second case, for nine.

In the first of these two experiments the red blood cell count fell from 1,240,000 cells to 890,000 cells and the hemoglobin dropped from 35 to 32 per cent during the period of feeding. No reticulocyte response occurred. However, the diameter of the erythrocytes diminished from 8.1 to 7.8 microns on the eighth day, rising again to reach 8.2 microns on the twelfth day. In the second experiment the red blood cell count was practically stationary throughout the nine days. The initial figure was 1,560,000, and the figure on the ninth day was 1,380,000. The hemoglobin was 40 per cent throughout. No reticulocyte response occurred, however; the diameter of the erythrocytes diminished again, and subsequently increased, just as in patients fed with liver. Before the experiment the average diameter was 8.5 microns, falling by the seventh day to 7.6 microns, and subsequently rising to 8.4 microns.

COMMENT

It has been pointed out briefly that various solutions of trypsin alone were not effective in the digestion of beef. The product of digestion when fed to patients with Addison-Biermer anemia did not produce any changes in the blood picture. When a solution of pepsin, hydrochloric acid and trypsin comparable to that which might be obtained from a normal stomach was used as a digestant, something was produced from the beef, which when fed to the patient produced definite changes in the blood picture. As only human gastric contents have heretofore proved potent in such feeding experiments, the results obtained are worthy of careful analysis, even though the number of experiments is relatively small.

In each of the first four experiments with our artificial gastic contents, there was an improvement in the red blood cell count and hemoglobin during the feedings. The tables show that the counts were stationary before each experiment, and were again stationary subsequent to the experiment. During the first feeding in case 1, case 2 and case 3, the erythrocytes increased at a rate of about 100,000 a day during the period of improvement, which is comparable to the rate of rise after liver therapy. In experiment 1 and in experiment 4 there

were reticulocyte rises of 5 and 4 per cent, respectively, and a change in red cell size, occurring at the same time during the feeding as that which occurs during successful liver therapy. In experiment 2 there was a prolonged reticulocyte response lasting about two weeks, and a rather delayed, but characteristic, alteration in erythrocyte diameters. In case 3, in which the initial red cell count was 2,820,000, no increase in reticulocytes occurred, but the changes in red cell size were pronounced. In the two cases in which very small amounts of trypsin were used, the blood was not improved, although changes occurred in the average diameter of the red corpuscles exactly like those in the other cases.

It is noteworthy that in each of four experiments in cases of hyperchromic macrocytic anemia of the so-called primary type, feedings of beef digested with artificial gastric contents, containing pepsin, hydrochloric acid and trypsin, produced changes in the blood comparable to those obtained by Castle when using human gastric contents to digest beef, except that there was a less pronounced reticulocyte response. It is of real significance that in each instance improvement in the red cell count and hemoglobin percentage, reticulocytosis and changes in the diameters of the red cells appeared coincident with the feedings, and ceased after the feedings were discontinued. Under such circumstances there can be little doubt that something was produced from the beef during the process of digestion that acted in the same way as the erythrocyte maturation factor contained in liver. As all the same changes in the red cell counts, the hemoglobin percentage, the reticulocyte percentage and the cell size occurred just as they take place during liver therapy, the same maturation factor must have been elaborated by digestion of the beef. The difference is that the changes are not all of the same magnitude as in adequate liver therapy, but duplicate the changes found when barely enough or not quite enough liver is fed. In other words, the maturation factor was produced, but not in sufficient quantity when compared to the successful administration of liver.

Assuming that digested beef can yield as much maturation factor as is contained in a like amount of liver, and certain of Castle's most successful experiments show that this is possible, many reasons may be advanced why our results are not as good as Castle's best or as good as those obtained with adequate liver treatment. Briefly, the following points are worthy of mention. Only 200 Gm. of beef were used, whereas at least 300 Gm. of liver are usually necessary. No special measures were taken to divide the beef muscle finely, as in Castle's experiments. No attempt was made during incubation to assure either optimum peptic or tryptic activity. A powdered preparation of trypsin was used which may have been inadequate in amount to complete diges-

tion, and which may not have been exactly comparable to the freshly activated enzyme in normal duodenal contents. Also, the patient in case 1 showed marked arteriosclerosis, which seems to be a barrier to the usually effective method of treatment, in that a larger dosage is required.[11] These points do not bear discussion at present and can be settled only by the results of further experiments. The important point to be made now is that *some maturation factor was produced.*

Returning to the original hypothesis that pancreatic insufficiency, notably a lack of trypsin production, is possibly related to the cause of Addison-Biermer anemia, just what do the results of our feeding experiments demonstrate? They show that tryptic digestion alone is no more effective than pepsin and hydrochloric acid alone, which was shown by Castle.[1] However, both these proteolytic enzymes together in solution are capable of producing from beef the substance necessary to bring about a remission in a case of macrocytic hyperchromic anemia. Furthermore, if very small amounts of trypsin are used with the activated pepsin, no remission occurs. If there is, then, an inadequate production of trypsin in a case of Addison-Biermer anemia during the stage of exacerbation, as well as a gastric achylia, and if beef digested by active pepsin and trypsin is capable of producing a remission in such a case, it seems probable that the fundamental disorder in Addison-Biermer anemia is a pancreatic insufficiency superimposed on gastric achylia, resulting in deficient protein digestion which is responsible for the anemia. Trypsin would then represent the unknown intrinsic factor of Castle, or, to be more accurate, the unknown extragastric factor of Morawitz.[12]

We have not proved such a hypothesis, but have made this preliminary report on the results of a few experiments in order that it may be more rapidly proved or disproved by the work of others, particularly as cases of untreated pernicious anemia suitable for necessary experimentation are now so rarely encountered. A great many questions will be raised about such a conception of the cause of Addison-Biermer anemia, which cannot be dealt with at present, but will be considered in a subsequent report.

SUMMARY

1. The present conception of Addison-Biermer anemia is that it is a deficiency disease due to an inadequate supply of a protein derivative necessary to normal maturation of red blood cells.

2. As a result of successful experiments in feeding beef digested with normal human gastric contents to patients with Addison-Biermer

11. Beebe, R. T., and Lewis, G. E.: Am. J. M. Sc. **181**:796, 1931.
12. Morawitz, P.: Arch. f. Verdauungskr. **47**:305, 1930.

anemia, Castle has concluded that the cause of the disorder is dependent on the gastric achylia. The nature of this supposed gastric defect has remained unproved, and he has termed it the unknown intrinsic factor.

3. Recent studies of the gastric contents during fasting and duodenal contents strongly suggest that in cases of Addison-Biermer anemia there is a marked insufficiency of the pancreatic enzymes, notably trypsin, in addition to the gastric achylia. The macrocytosis characteristic of this anemia has also been frequently observed in pancreatic disorders.

4. Feeding experiments in which solutions of trypsin were used to digest beef have failed to produce any effect on the blood findings in cases of Addison-Biermer anemia.

5. Feeding experiments in which an artificial gastric content containing hydrochloric acid, pepsin and trypsin was used to digest beef have in three instances in two cases of Addison-Biermer anemia and in one instance in a case of sprue with a similar blood picture produced changes in the red blood cell count, hemoglobin determinations and reticulocyte response similar to those obtained by Castle.

6. Changes in the average diameter of the red cells characteristic of a beginning remission after liver therapy occurred in these four instances and also in two others when very small amounts of trypsin were used. No other evidence of improvement in the blood findings was detected in the last two cases.

7. Our feeding experiments show that beef digested by hydrochloric acid, pepsin and trypsin yields the erythrocytic maturation factor necessary to produce all the blood changes characteristic of a remission in pernicious anemia. The changes demonstrated are not as pronounced as those in adequate liver therapy, but are on the whole more like those in inadequate treatment with liver.

8. It seems probable that the protein derivative deficiency in Addison-Biermer anemia is due to a lack of both peptic and tryptic digestion. Trypsin would then represent the unknown intrinsic factor of Castle.

THIOCYANATE THERAPY IN HYPERTENSION

II. ITS EFFECT ON BLOOD PRESSURE

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The reintroduction of thiocyanate in the treatment for arterial hypertension has, in recent years, attracted wide attention. A number of investigators have attested to its effectiveness in lowering both normal and abnormally elevated blood pressures.[1] On the other hand, it has been stated that in a large group, thiocyanate appears to exert no more beneficial effect on hypertension than do certain so-called nonspecific measures of therapy, classed under the general heading of "psychic and sedative treatment."[2] We have shown in a previous study[3] that thiocyanate administered in the dosage frequently recommended may be accompanied by serious toxic manifestations and even death. Furthermore, the great tendency toward variability of raised blood pressures[4] and the not infrequent spontaneous remissions observed in the course of essential hypertension[5] often render the true interpretation of any so-called therapeutic endeavor particularly hazardous. It therefore

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1. Gager, L. T.: The Incidence and Management of Hypertension, with a Note on Sulphocyanate Therapy, J. A. M. A. **90**:82 (Jan. 14) 1928. Westphal, K., and Blum, R.: Rhodan Treatment of Genuine High Arterial Pressure and the Theoretical Foundation for It, Deutsches Arch. f. klin. Med. **152**:331, 1926. Nichols, J. B.: Pharmacologic and Therapeutic Properties of the Sulphocyanates, Am. J. M. Sc. **170**:735 (Nov.) 1925.

2. Ayman, D.: An Evaluation of Therapeutic Results in Essential Hypertension: I. The Interpretation of Symptomatic Relief, J. A. M. A. **95**:246 (July 26) 1930.

3. Goldring, W., and Chasis, H.: Thiocyanate Therapy in Hypertension: I. Observations on Its Toxic Effects, Arch. Int. Med. **49**:321 (Feb.) 1932.

4. Mosenthal, H. O., and Short, J. J.: The Spontaneous Variability of Blood Pressure and the Effects of Diet upon High Blood Pressure with Special Reference to Sodium Chloride, Am. J. M. Sc. **165**:53, 1923. Diehl, H. S.: The Variability of Blood Pressure: Morning and Evening Studies, Arch. Int. Med. **43**:835 (June) 1929.

5. Ayman, D.: Normal Blood Pressure in Essential Hypertension, J. A. M. A. **94**:1214 (April 19) 1930.

seemed advisable to us that another series of observations be added to those reported by other investigators, in order to add to the sum total of such observations and to determine, if possible, the range of effective dosage by interpreting as effective only distinctly unequivocal instances of lowering of blood pressure; finally, to make such observations on the excretion of thiocyanate in individual patients as were deemed necessary in order to arrive at a quantitative estimate of the amount of residual drug in the body at the time of its first observed effect on the blood pressure.

PLAN OF STUDY AND METHOD

Fifty patients with hypertension were selected and subjected to seventy-four different trials with thiocyanate therapy. Of these trials, sixty-nine were with patients who had hypertension of the essential type and five were with patients whose hypertension was associated with chronic diffuse glomerulonephritis. Forty-four trials were made in the outpatient clinic and thirty were made during a stay in the hospital wards. All blood pressure readings were made by the same group of observers. Readings were consistently taken on the right arm only, and a standard mercury manometer was used exclusively. The auscultatory method was invariably employed. A sufficient period of mental and physical rest was uniformly insisted on before blood pressure readings were made. With the arm cuff in position, five and often more readings were made before the blood pressure level was decided on. When for any reason doubt existed or when a decided change from the previous reading was noted, two and usually three observers made independent readings before a final estimate of the blood pressure level was accepted. While on thiocyanate therapy, outpatients were seen weekly and ward patients at least once daily.

Being aware of the great tendency toward spontaneous variability of blood pressure levels, control periods were extended as long as feasible, and as many blood pressure readings were made as we believed were necessary on each patient. The length of the control period was principally determined by the history of known duration of the hypertension and the degree of variability of the blood pressure noted under our own observation. That is, the longer the history of hypertension as obtained from the patient and the less the variability of the blood pressure under our observation, the relatively shorter control period seemed necessary.

Both the sodium and potassium salts were used indiscriminately in our series, and no record was kept of the particular salt administered to each patient. Such a record did not seem necessary in view of the evidence that the effective radical is the thiocyanate.[6]

6. Nichols (footnote 1, third reference).

The principal purpose of this study was to investigate the depressor effect of thiocyanate on the blood pressure in persons with hypertension. It was necessary then to decide on some criterion by which this effect could be measured. Two alternatives presented themselves. The first criterion that suggested itself was a predetermined fall, in millimeters of mercury, in both systolic and diastolic pressures. It was obvious early in our study that this criterion of effect would not be wholly adequate, because even appreciable falls in blood pressure from a very high pretreatment level might not constitute a satisfactory clinical reduction, as, for example, a fall in systolic pressure from 260 to 210 mm. of mercury or a fall in diastolic pressure from 140 to 115 mm. Moreover, there are instances in which a considerable and persistent fall from the control level occurs in the systolic pressure, whereas the fall in the diastolic pressure is insignificant. This occurrence is not infrequent when the pretreatment level of the systolic pressure is considerably elevated above normal and the diastolic only slightly. Such a response, we believe, must obviously be accredited to the therapy employed, but if the aforementioned criterion were used, it would have to be regarded as an unsuccessful trial. The second alternative was to use as a criterion a definite level of systolic and diastolic blood pressures, a fall to or below which, after treatment, would be termed a successful depressor effect. We decided to use this criterion and selected arbitrarily the level of 165 systolic and 100 diastolic. On the face of it, it may appear that in some instances the therapy was considered as effective even though only slight falls occurred from the control level of pressure to the "criterion" level. Actually, as the tables show, this was not the case. The average of all "successful" falls in systolic pressure amounted to 45 mm. of mercury and in the diastolic pressure it amounted to 31 mm.

The method employed in estimating the quantitative excretion of thiocyanate in the urine and its accuracy as compared with the method described by Schreiber [7] were noted in a previous paper by us.[3]

In order to evaluate further the effectiveness of thiocyanate as a depressor drug, strict interpretation was applied to the meaning of the term "trial." In the early part of the study a "trial" was considered complete only when the drug had lowered blood pressure, in accordance with our stated criteria, or when toxic symptoms occurred. The relatively frequent occurrence of toxic manifestations in our early cases suggested the necessity for modifying our stand in the interests of safety to the patient. Accordingly in the patients studied in the latter part of this series a "trial" was considered complete if neither thera-

7. Schreiber, H.: Thiocyanate Content of Human Blood Serum, Biochem. Ztschr. **163**:241, 1925.

peutic nor toxic effect occurred when 0.163 Gm. (2½ grains) had been given for seventy-seven consecutive days or more, if 0.326 Gm. (5 grains) had been given for eighteen consecutive days or more or if 0.652 Gm. (10 grains) had been given for twelve consecutive days or more. In the three instances in which 1 Gm. or more was given daily,

TABLE 1.—*Results of Treatment with Thiocyanate in Essential Hypertension: Ambulatory Group*

No.	Age	Blood Pressure Control		Control Period, Days	Lowest Blood Pressure after Treatment	Thiocyanate Intoxication	Effective in Lowering Blood Pressure
		Range, Mm. Hg	Average, Mm. Hg				
1	54	220/110 to 198/104	213/107	126	150/ 85	No	Yes
2	54	220/110 to 190/104	190/104	161	165/ 90	No	Yes
3	64	220/120 to 185/100	205/109	35	140/ 70	No	Yes
4	65	230/138 to 175/104	203/116	294	190/ 92	Yes	No
5	46	260/130 to 210/110	232/120	378	185/ 95	No	No
6	56	205/120 to 170/ 98	180/105	231	135/ 70	Yes	Yes
7	37	240/140 to 188/106	203/122	273	158/ 95	No	Yes
8	53	236/156 to 198/120	220/136	182	157/ 90	No	Yes
9	53	215/125 to 175/115	196/117	35	150/ 75	No	Yes
10	53	205/120 to 174/105	190/113	14	145/ 90	No	Yes
11	29	268/132 to 180/132	206/132	133	180/125	No	No
12	29	268/132 to 180/132	198/132	168	185/125	Yes	No
13	29	268/132 to 180/132	190/130	203	150/110	No	No
14	50	210/120 to 160/108	174/112	33	155/ 95	No	No
15	42	250/160 to 132/ 80	187/122	53	207/127	No	No
16	38	182/145 to 168/135	177/140	14	180/125	No	No
17	58	212/122 to 196/109	203/116	84	165/105	No	No
18	61	224/130 to 198/110	210/119	35	192/105	No	No
19	62	240/125 to 200/ 96	217/109	91	158/ 90	No	Yes
20	51	222/142 to 216/140	218/141	28	184/112	No	No
21	46	250/118 to 195/100	222/109	62	184/ 90	No	No
22	64	210/ 88 to 190/ 88	198/ 88	32	150/ 75	No	Yes
23	53	230/125 to 170/110	206/121	48	170/ 98	No	No
24	40	250/130 to 232/120	239/123	42	186/106	No	No
25	46	225/110 to 184/ 96	209/103	84	190/100	No	No
26	62	206/100 to 188/ 92	200/ 96	28	164/ 82	No	No
27	65	212/110 to 160/ 90	186/101	111	178/ 94	No	No
28	54	212/104 to 198/ 94	206/ 97	42	170/ 90	No	No
29	45	200/128 to 185/102	192/115	56	174/ 96	No	No
30	54	210/118 to 165/100	182/100	133	188/108	No	No
31	42	160/125 to 150/108	156/116	21	178/110	No	No
32	51	250/158 to 184/110	243/129	203	164/120	No	No
33	55	250/140 to 180/ 98	200/116	67	156/ 96	No	No
34	62	235/130 to 180/115	208/123	28	215/110	No	No
35	46	260/130 to 185/ 92	215/110	469	166/ 90	No	No
36	64	215/120 to 160/180	200/105	28	150/ 72	No	No
37	63	230/138 to 175/ 95	205/110	220	190/ 90	No	No
38	54	220/120 to 165/100	195/105	168	175/108	No	No
39	46	250/118 to 170/ 94	185/102	54	176/110	No	No
40	64	216/ 96 to 184/ 78	199/ 88	91	142/ 70	No	Yes
41	50	218/126 to 212/122	215/124	7	182/100	No	No
42	53	220/120 to 170/ 98	180/110	90	200/112	No	No
43	40	234/128 to 186/106	205/105	180	186/104	No	No
44	56	230/125 to 180/100	209/119	360	190/ 90	Yes	No

the drug was discontinued because of toxic symptoms in two and a fall in blood pressure in one. In every instance in which we discontinued thiocyanate before either a therapeutic or a toxic effect occurred, the total amount that had been administered was, with few exceptions, greater than the amount frequently reported by others as an effective dosage.

RESULTS

Tables 1 and 2 give a summary of the results of treatment with thiocyanate in an ambulatory and a hospitalized group of patients with

essential hypertension. There were forty-four trials in the ambulatory group and twenty-five trials in the hospital group. The ages ranged from 29 to 65 years. The period of control in the ambulatory group ranged from seven to three hundred and seventy-eight days and in the hospital group from five to one hundred and five days. It will be noted

TABLE 2.—*Results of Treatment with Thiocyanate in Essential Hypertension: Hospitalized Group*

No.	Age	Blood Pressure Control: Range, Mm. Hg	Blood Pressure Control: Average, Mm. Hg	Control Period, Days	Lowest Blood Pressure after Treatment	Thiocyanate Intoxication	Effective in Lowering Blood Pressure
1	50	210/120 to 160/108	174/112	15	160/100	No	No
2	53	232/134 to 198/125	209/129	8	129/ 70	No	Yes
3	46	208/120 to 190/108	194/114	35	170/110	No	No
4	57	230/130 to 186/ 92	202/113	11	118/ 90	Yes	Yes
5	53	236/134 to 196/120	220/113	16	146/ 74	No	Yes
6	53	230/130 to 220/106	224/113	7	210/120	Yes	No
7	55	180/105 to 158/ 95	174/102	12	115/ 80	No	Yes
8	56	220/130 to 190/100	207/110	8	158/ 90	Yes	Died*
9	40	225/130 to 204/100	237/112	13	204/ 88	Yes	Died*
10	63	210/146 to 190/128	202/133	5	140/ 80	Yes	Yes
11	50	250/155 to 216/120	230/130	18	180/100	No	No
12	50	230/130 to 186/100	205/110	47	190/120	Yes	No
13	63	240/168 to 190/128	215/145	31	138/ 70	No	Yes
14	52	228/138 to 208/104	221/122	8	182/ 90	No	No
15	55	250/140 to 198/120	227/137	12	180/100	No	No
16	55	250/140 to 180/ 98	200/110	105	210/114	Yes	No
17	49	260/140 to 190/ 96	204/114	25	180/ 98	No	No
18	43	198/132 to 170/112	181/126	14	148/ 86	No	Yes
19	46	200/100 to 185/ 95	187/109	26	162/ 92	No	No
20	48	208/118 to 178/108	195/115	13	186/ 98	No	No
21	44	168/114 to 154/ 92	159/103	9	162/ 90	Yes	No
22	54	264/132 to 240/120	253/128	9	164/ 84	Yes	Yes
23	51	182/120 to 162/ 98	173/ 98	19	140/ 88	No	No
24	48	198/160 to 184/ 98	200/119	17	184/ 96	No	No
25	51	250/158 to 192/118	221/124	11	196/110	No	No

* Death was due to thiocyanate poisoning.[3]

TABLE 3.—*Results of Treatment with Thiocyanate in Nephritic (Chronic Diffuse Glomerulonephritis) Hypertension*

No.	Age	Blood Pressure Control: Range, Mm. Hg	Blood Pressure Control: Average, Mm. Hg	Control Period, Days	Lowest Blood Pressure after Treatment	Thiocyanate Intoxication	Effective in Lowering Blood Pressure
1	21	220/140 to 180/120	196/130	7	114/ 64	No	Yes
2	44	290/180 to 234/156	260/165	9	138/ 95	No	Yes
3	47	248/160 to 202/125	229/141	8	160/100	No	Yes
4	60	210/110 to 176/ 90	195/ 98	150	194/ 86	No	No
5	60	210/110 to 176/ 90	195/ 95	143	170/ 86	No	No

that a "trial" was considered effective when the blood pressure fell to or below 165 systolic and 100 diastolic, that is, the arbitrarily chosen criterion. There are instances (see cases 20, 24 and 41, table 1, and cases 11, 14 and 15, table 2) in which marked falls in both systolic and diastolic pressures occurred, but the blood pressure remained distinctly above 165 systolic and 100 diastolic, and no improvement occurred in the subjective symptoms. In order to adhere to our strict standard of criteria for effect, all these instances, because of the difficulty of their

interpretation, were considered ineffective. Table 3 shows the effect of thiocyanate on the hypertension of chronic diffuse glomerulonephritis. It represents five trials on four patients. It is interesting, even in the small number, that notwithstanding reports to the contrary, thiocyanate carefully administered appears just as likely to be effective and no more likely to produce toxicity in patients with glomerulonephritis than in patients with essential hypertension. In this group, care was taken not to include patients during an acute exacerbation because of the possibility of an accompanying spontaneous fall of blood pressure as the acute condition subsides. It may seem that the control period of from seven to nine days in the so-called "effective" cases was too short to be conclusive. But that thiocyanate did actually lower the blood

TABLE 4.—*Persistence of Hypotensive Effect of Thiocyanate*

No.	Type of Hypertension	Average Daily Dose, Gm.	Total Dose, Gm.	Persistence, Days
Ambulatory group				
1	Essential	0.326	8.48	28
2	Essential	0.326	10.76	26
3	Essential	0.652	13.69	49
4	Essential	0.326	15.98	34
5	Essential	0.326	29.35	110
6	Essential	0.489	31.96	55
7	Essential	0.326	33.66	48+
8	Essential	0.489	75.50	41
Hospitalized group				
9	Essential	0.326	4.56	28+
10	Essential	0.652	8.48	15+
11	Nephritic	0.652	9.29	14
12	Nephritic	0.978	10.43	73+
13	Essential	1.192	26.35	7
14	Essential	0.613	31.14	22

pressure in at least one patient was obvious from the fact that the blood pressure returned to its original level fourteen days after the drug was discontinued. In the two other patients the blood pressure remained low up to the time the patients left the hospital at their own request.

Table 4 represents follow-up observations on fourteen patients in whom the blood pressure was effectively lowered by thiocyanate and the duration of the hypotensive effect after discontinuance of the drug. The hypotensive effect in this group of patients persisted for from seven to one hundred and ten days, at which time the blood pressure had returned to or nearly to its control level. There seemed to be no constant relationship between the persistence of the artificially lowered blood pressure and the amount of thiocyanate required to produce the lowering.

Table 5 serves to indicate that the effect of thiocyanate cannot be logically anticipated from the average daily dose or the duration of medication. It will be seen that a "trial" was considered completed when

TABLE 5.—*Relation of the Dosage of Thiocyanate to the Effect on Blood Pressure and the Occurrence of Toxic Manifestations*

No.	Type of Hypertension	Blood Pressure Lowered to or Below 165/100, Mm. Hg	Average Daily Dose, Gm.	Duration of Medication, Days	Total Dose, Gm.	Toxic Effect
1	Essential	Yes	0.326	14	4.56	No
2	Essential	Yes	0.652	7	4.56	No
3	Essential	Yes	0.326	14	4.56	No
4	Essential	No	0.326	18	5.87	No
5	Essential	No	0.652	9	5.87	Psychosis
6	Essential	No	0.978	7	6.85	No
7	Essential	No	0.326	25	8.15	No
8	Essential	No	0.815	10	8.15	Nausea, vomiting
9	Essential	Yes	0.326	27	8.80	No
10	Essential	No	0.326	28	9.13	No
11	Essential	No	0.652	14	9.13	No
12	Essential	Yes	0.326	28	9.13	Psychosis
13	Essential	Yes	0.978	10	9.78	No
14	Essential	No	0.652	15	9.78	Death*
15	Essential	No	0.326	33	10.76	No
16	Essential	No	0.405	28	11.34	Fatigue
17	Essential	No	1.620	7	11.34	Psychosis
18	Essential	Yes	0.326	35	11.41	No
19	Essential	No	0.326	35	11.41	No
20	Essential	No	0.326	35	11.41	No
21	Essential	No	0.170	69	11.73	Dermatitis
22	Essential	No	0.978	12	11.74	No
23	Essential	No	0.978	12	11.74	No
24	Essential	No	0.163	77	12.55	No
25	Essential	No	0.978	13	12.71	Psychosis
26	Essential	No	0.326	40	13.04	No
27	Essential	No	0.652	20	13.04	No
28	Essential	No	0.326	40	13.04	No
29	Essential	Yes	0.691	19	13.13	No
30	Essential	No	0.326	42	13.69	No
31	Essential	Yes	0.652	21	13.69	No
32	Essential	No	0.326	42	13.69	No
33	Essential	No	0.326	42	13.69	No
34	Essential	Yes	0.326	43	14.01	Fatigue, nausea
35	Essential	Yes	0.805	18	14.49	Death*
36	Essential	No	0.326	49	15.97	No
37	Essential	Yes	0.326	49	15.97	No
38	Essential	No	0.489	35	17.11	Fatigue, nausea
39	Essential	No	0.326	55	17.93	No
40	Essential	No	0.652	28	18.26	No
41	Essential	No	0.652	28	18.26	No
42	Essential	No	0.163	121	19.72	No
43	Essential	No	0.326	63	20.54	No
44	Essential	Yes	0.326	66	21.51	No
45	Essential	Yes	0.326	69	22.49	No
46	Essential	Yes	0.326	70	22.82	No
47	Essential	No	0.326	71	23.15	No
48	Essential	No	0.163	148	24.12	No
49	Essential	No	0.326	75	24.45	No
50	Essential	No	0.326	77	25.10	No
51	Essential	No	0.326	77	25.10	No
52	Essential	Yes	0.326	78	25.42	No
53	Essential	No	0.489	52	25.43	No
54	Essential	No	0.648	41	26.57	No
55	Essential	Yes	1.210	22	26.62	Psychosis
56	Essential	No	0.652	41	26.73	No
57	Essential	No	0.652	42	27.38	No
58	Essential	No	0.326	84	27.38	No
59	Essential	No	0.652	42	27.38	No
60	Essential	No	0.652	49	31.95	No
61	Essential	Yes	0.638	51	32.54	Psychosis
62	Essential	No	0.652	50	32.60	No
63	Essential	Yes	0.978	35	34.27	No
64	Essential	Yes	0.652	55	35.86	No
65	Essential	No	0.652	55	35.86	No
66	Essential	No	0.578	78	45.08	No
67	Essential	No	0.652	74	48.25	No
68	Essential	No	0.652	100	65.20	No
69	Essential	No	0.326	203	66.18	No
70	Glomerulonephritis	Yes	0.326	19	6.19	No
71	Glomerulonephritis	Yes	0.978	10	9.78	No
72	Glomerulonephritis	Yes	1.080	10	10.80	No
73	Glomerulonephritis	No	0.326	64	20.86	No
74	Glomerulonephritis	No	0.652	76	49.55	No
1	Normal blood pressure	Yes†	0.652	5	3.26	No
2	Normal blood pressure	Yes†	0.326	14	4.56	No
3	Normal blood pressure	Yes†	0.978	5	4.89	No
4	Normal blood pressure	Yes†	0.326	36	11.74	No

* Death due to thiocyanate poisoning.

† The fall after treatment with thiocyanate was unequivocal and persistent for from two to ten days.

the blood pressure fell in accordance with our stated criterion, when toxic symptoms occurred or when the total amount of thiocyanate administered was in most instances distinctly greater than the amount usually recommended by others as therapeutically effective.[8] The latter course, namely, discontinuance of the thiocyanate before either therapeutic or toxic manifestations occurred after a relatively large dose had been administered, seemed imperative to us because of our previous experience with the toxicity of thiocyanate.[3] The toxic manifestations noted in this table are fully described in the study referred to. This table further indicates the frequency with which thiocyanate may lower normal blood pressure.

In table 6, the data of the preceding table are condensed and summarized. They represent an evaluation of the clinical usefulness of various dosages of thiocyanate. The absence of therapeutic effect with

TABLE 6.—*Effectiveness of Thiocyanate with Various Daily Dosages*

Daily Dose, Gm.	Number of Trials	Blood Pressure Lowered to or Below 165/100, Mm. Hg	Effectiveness, per Cent	Number of Toxic Cases	Thiocyanate Intoxication, per Cent	Number of Fatal Cases Due to Thiocyanate Poisoning
0.163 (2½ grains)	4	0	0	1*	25	0
0.326 (5 grains)	34	12	35.2	3	8.8	0
0.489-0.815 (7.5-12.5 grains)	26	6	23	6	23	2
0.978-1.63 (15-25 grains)	10	5	50	3	33.3	0

* Maculopapular dermatitis.

0.163 Gm. (2½ grains) daily administered from seventy-seven to one hundred and forty-eight days in four patients seemed sufficient reason for considering it an ineffective dosage. The great frequency of toxic manifestations with from 0.978 to 1.62 Gm. (from 15 to 25 grains) given daily in ten trials was sufficient evidence for considering this dosage harmful. The dosage of from 0.489 to 0.815 Gm. daily (from 7½ to 12½ grains) was accompanied by toxic manifestations in the same percentage as it produced satisfactory lowering of the blood pressure. Moreover, two fatalities occurred in this group as a result of thiocyanate poisoning. The highest percentage of effectiveness with the lowest incidence of toxicity was observed in those patients who received 0.326 Gm. (5 grains) daily.

The data in table 7 indicate the relative excretion rate of thiocyanate in patients with essential hypertension and in patients with the hyper-

8. Gager (footnote 1, first reference). Palmer, R. S.; Silver, L. S., and White, P. D.: The Clinical Use of Potassium Sulphocyanate in Hypertension, New England J. Med. **201**:709 (Oct. 10) 1929. Borg, J. F.: Use of Sulphocyanates in Treatment of Hypertension, Minnesota Med. **13**:281 (May) 1930.

tension of chronic diffuse glomerulonephritis. Furthermore, when the same amount of thiocyanate was administered in a single dose to a "normal" person and one with chronic diffuse glomerulonephritis, the "normal" person excreted an average daily amount twice as great as did the patient with nephritis. It would seem from these observations that the ease with which thiocyanate is excreted bears a direct relation-

TABLE 7.—*A Comparison of the Excretion Rate of Thiocyanate in Essential Hypertension and Nephritic Hypertension* *

No.	Type of Hypertension	Average Daily Dose, Gm.	Average Thiocyanate Excretion, Gm. per 24 Hr.
1	Nephritic	0.978	0.097
2	Nephritic	1.004	0.277
3	Nephritic	0.652	0.230
4	Essential	0.978	0.540
5	Essential	0.915	0.557
1	Normal	1.143 (single dose)	0.088
2	Nephritic	1.143 (single dose)	0.043

* Chronic diffuse glomerulonephritis.

TABLE 8.—*Excretion Time of Thiocyanate (Single Dose)*

Diagnosis	One Dose, Gm.	Days Necessary for Complete Excretion
Normal*	0.163	5
Normal	0.163	4
Normal	0.163	4
Normal	0.163	4
Normal	0.326	9
Normal	0.652	11
Normal	1.143	14
Nephritist	1.143	22

* No evidence of organic disease.
† Chronic diffuse glomerulonephritis.

TABLE 9.—*Summary of Results of Treatment with Thiocyanate*

	Number of Trials	Blood Pressure Lowered to or Below 165/100, Mm. Hg	Effectiveness in Lowering Blood Pressure, per Cent	Toxic	Deaths Due to Thiocyanate Poisoning[3]
"Normal"*	4	4	100	0	0
Essential hypertension	69	20	28.9	13	2
Nephritic hypertension	5	3	60	0	0
Hypertension, total	74	23	31	13	2

* In this group of persons with "normal" blood pressure the fall after treatment with thiocyanate was unequivocal and persistent for from two to ten days.

ship to the functional integrity of the kidney. Likewise, there appears to be a distinct lack of relationship between the average amount excreted per day and the average amount administered per day. The slow excretion rate of thiocyanate in the presence of glomerulonephritis is reflected in the prolongation of its time for complete excretion as

compared with a "normal" person. This is shown in table 8. The remaining data in this same table clearly indicate that the days necessary for complete excretion of the drug are roughly proportional to the total amount administered. The observation that at least four days are necessary for the complete excretion of a single dose as small as 0.163 Gm. (2½ grains), in persons with normal renal function, is striking evidence of the great ease with which thiocyanate accumulates in the body on continuous administration over a period of time.

Table 9 is a summary of the results of thiocyanate administration in the entire group studied. The blood pressure was definitely and effectively lowered in 31 per cent of all hypertensive cases observed. The fall in blood pressure was almost invariably associated with improvement in subjective symptoms. The higher percentage of effectiveness in the group with glomerulonephritis has little significance in view of the small number observed. The toxic and fatal cases noted in this table were fully discussed in a previous paper.[9]

COMMENT

In recent years a number of substances have been advocated as useful in artificially lowering the blood pressure in hypertension.[9] Their effectiveness in this regard has not been generally confirmed. Thiocyanate, on the other hand, has met with approval among a large number of independent investigators. One fact seems true from our data: thiocyanate will effectually lower blood pressure in one of about every three persons with hypertension. Our percentage of effectiveness is lower than that observed by many other investigators. Almost invariably, a fall in blood pressure was accompanied by subjective improvement. However, subjective improvement occurred in many patients on thiocyanate therapy in whom no lowering of blood pressure occurred. This led us to believe that such improvement was largely psychic. Still, exclusive of toxic effects from the drug itself, no obvious harmful effects were noted from persistent lowering of a previously high blood pressure. Whether or not harmful effects occurred that were not immediately obvious, we cannot say from the data available.

When it is thought that thiocyanate may be useful in a given patient, the dose should not exceed 0.362 Gm. (5 grains) daily. However, the uncertainty of its effect is evidenced by the fact that such daily dosage

9. Macdonald, W. J.: Extractives of Liver Possessing Blood Pressure Lowering Properties, Canad. M. A. J. **15**:697, 1925. Barksdale, I. S.: Studies on the Blood Pressure Lowering Principle in the Seed of the Watermelon (Cucurbita Citrullus), Am. J. M. Sc. **171**:111, 1926. Stieglitz, E. J.: Bismuth Subnitrate in the Treatment of Arterial Hypertension, J. A. M. A. **95**:842 (Nov. 12) 1930.

may be effective in lowering blood pressure in as short a period as fourteen days or it may be necessary to continue it as long as seventy-eight days. At the first indication of toxic effect (fatigue, nausea or vomiting) or the first distinct fall in blood pressure, the drug should be discontinued. When the blood pressure, having responded by a satisfactory fall, returns to its original high level, thiocyanate may be safely readministered only when ferric chloride added to the acidified urine indicates that the drug has been entirely excreted. If the blood pressure does not show a satisfactory fall after 26.16 Gm. (5 grains daily for eighty days) has been taken, our data indicate that with few exceptions it is useless to continue the treatment.

The foregoing scheme of dosage is purely arbitrary and based on a consideration of our entire series as a group. However, in considering individual patients, it must be concluded that there is no constant dosage at which either a toxic or a therapeutic effect may be anticipated. Some of the inconstancies observed are illustrated by the following observations: One patient who responded, by a fall in blood pressure, to 0.326 Gm. (5 grains) daily on three successive occasions failed subsequently to respond to a repetition of treatment with the same dosage over a similar period of time. Another patient who responded, by a satisfactory fall in blood pressure, to 0.326 Gm. (5 grains) given daily on two different occasions failed subsequently to respond to 0.652 Gm. (10 grains) daily given over a comparable period of time. A third patient who responded satisfactorily after a total dose of 13.2 Gm. (202 grains) subsequently became severely toxic (hallucinations of sight and hearing, disorientation, etc.) on a total dose of 12.74 Gm. (195 grains).

It is this uncertainty regarding proper dosage, coupled with the fact that frequently there is slight if any difference between the amounts that produce therapeutic and toxic effects, that leads us to believe that thiocyanate will have a much restricted usefulness in clinical medicine.

SUMMARY

Data are presented on fifty patients subjected to seventy-four trials with thiocyanate therapy. In forty-six of these patients the hypertension was of essential type, and in the remaining four patients it was associated with chronic diffuse glomerulonephritis. Forty-four trials were made in the outpatient clinic and thirty with the patients confined to the hospital.

Observations were made on the daily excretion rate of thiocyanate in the urine and the number of days necessary for its complete elimination after continuous medication and after a single dose in patients with essential hypertension and nephritic hypertension and in normal persons.

Toxic effects of thiocyanate were not observed in four patients with chronic diffuse glomerulonephritis, three of whom responded by a satisfactory fall in blood pressure.

Therapeutic, toxic or fatal effects could not be anticipated from the amount of the drug administered.

The dosage found to be most effective in lowering blood pressure and least often attended by toxic manifestations was 0.326 Gm. (5 grains) given daily over a period of from fourteen to seventy-eight days.

Thiocyanate was 31 per cent effective in lowering blood pressure in this series.

Toxic manifestations occurred in thirteen patients, or 17 per cent of the total group studied.

CINCHOPHEN HEPATITIS

AN EXPERIMENTAL STUDY

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Numerous reports in the recent medical literature refer to evidences of severe liver damage, not infrequently resulting in death, in patients given cinchophen as the chief or sole therapeutic agent. This drug, originally introduced in 1908 as a mobilizer of uric acid and advocated for the relief of gout, has come to be commonly utilized as an analgesic, particularly for the relief of pain of rheumatic type. The more common use of this drug makes a further understanding of its toxic action highly desirable.

A few references were made to toxic reactions, such as the tendency to cause urticaria or digestive disturbances,[1] early in the use of this drug, but the possibility of serious consequences was not appreciated until recently. Cabot,[2] in 1925, first reported a death with acute hepatic atrophy following the use of cinchophen. A report on "The Specific Character of Toxic Cirrhosis as Observed in Cinchophen Poisoning"[3] has recently been given by Beaver and Robertson. They presented a review of the literature and an analysis of the pathologic changes found in five patients who died following cinchophen therapy. They found the changes in the liver to agree with the concept of a "toxic cirrhosis."

Cinchophen has been employed for several years as an aid in roentgen studies of the gallbladder due to an increased rate of accumulation of opaque halogenated phthaleins in the bile following the administration of cinchophen. Brugsch and Horsters[4] first called attention,

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From the Laboratory of Pharmacology, University of Oregon Medical School.

1. Herrick, W. W.: A Scarlatiniform Rash from Atophan, J. A. M. A. **61**:1376 (Oct. 11) 1913. Phillips, John: Skin Rashes Following the Administration of Atophan, ibid. **61**:1040 (Sept. 27) 1913.

2. Cabot, R. C., and Cabot, Hugh: Case Records of the Massachusetts General Hospital, Boston M. & S. J. **192**:1122, 1925.

3. Beaver, D. C., and Robertson, H. E.: The Specific Character of Toxic Cirrhosis as Observed in Cinchophen Poisoning, Am. J. Path. **7**:237 (May) 1931.

4. Brugsch, T., and Horsters, H.: Ueber die Leber als Ausscheidungsorgan und über die Wirkung der Choleretika, insbesondere des Atophans, Med. Klin. **20**:661 (May 18) 1924.

in 1924, to the increased secretion of bile following the use of the ethyl ester of paramethylphenyl cinchoninic acid. Chabrol and Maximin,[5] utilizing animals with fistulas of the common duct, with the cystic duct tied off, reported a fivefold increase in the secretion of bile following the injection of cinchophen. The relative change in biliary constituents found following the injection of cinchophen, together with the marked increase in the flow of bile, might well be interpreted as evidencing an irritation of the hepatic parenchyma. No other agent used in their study approached the cholagogue activity of cinchophen.

EXPERIMENTAL WORK

An experimental study of the possible influence of cinchophen on the liver seemed highly desirable in view of the facts stated. The icterus index of the serum and urobilinogen of the urine were determined in four dogs and eight rabbits. These indicators of hepatic function gave values within the normal range in each instance. A section of liver was then removed under morphine analgesia and local anesthesia in order to avoid any hepatic disturbance from systemic anesthesia. These biopsy specimens were considered control material for the respective animals. Four rabbits and the four dogs were then given daily doses of cinchophen by mouth. The drug was mixed with the food given the rabbits and was administered in enteric capsules to the dogs. Thirty milligrams per kilogram of weight was considered in keeping with the therapeutic dose for man. One dog was given the therapeutic dose; two were given twice this amount, and another received five times the therapeutic dose. The rabbits were each given ten times the calculated therapeutic dose. The drug was given to the dogs for seventeen days, while the rabbits received it for forty-five days. Another section of liver was removed at the completion of the administration of cinchophen, and additional sections were removed from the dogs following a period allowed for recovery. Sections of the liver were removed from four rabbits kept under similar conditions but not given any drug, at the beginning and end of the experimental period, these sections serving as control checks on the sections from the experimental animals.

The department of pathology of the medical school prepared the sections of liver removed from all the animals. Dr. Warren C. Hunter, assistant professor of pathology, expressed the following opinion concerning the histologic appearance of the sections:

> The cytological alterations in the livers of both rabbits and dogs receiving different multiples of the therapeutic dose of cinchophen were identical in kind

5. Chabrol, E., and Maximin, M.: Recherches experimentales sur les cholagogues administres per voie veineuse, Presse méd. **37**:666 (May 22) 1929.

but varied somewhat in degree according to the amount of drug administered. It would appear also that dogs are more susceptible to cinchophen than rabbits since the evidence of liver damage was approximately the same in rabbits that received larger amounts per kilogram weight for a period approximately three times as long as that in which the dogs received the drug.

When compared to the normal biopsy control section in individual cases, the following changes were detected in the liver: for a variable distance about the central veins the cytoplasm of the hepatic cells had lost the normal finely reticular-granular structure and appeared as coarse, distinctly separated granules between which the delicate reticulum was lacking. Although at times indistinct, the cell borders were still intact and there was no actual fragmentation or autolysis. Fat stains gave negative results. The nuclei exhibited constantly some degree of chromatolysis and rather commonly contained a single, prominent nucleolus, not often encountered in control material. Mitotic activity was lacking.

The lesions in the liver sections removed from the dogs proved to be identical with those in the rabbits. In the dogs allowed a recovery period after stopping the drug it was found that with one exception (dog no. 2), the damage had been recovered from. The liver of dog no. 2 still manifested evidence of liver injury but no cirrhotic changes were noted.

Dog 2 had received the largest dose of cinchophen, five times the calculated therapeutic amount, which might well account for the remaining evidence of liver damage approximately one month following cessation of the administration of cinchophen. Glycogen stored in the liver has been shown to protect that organ against the toxic action of chloroform.[6] The relative resistance of the rabbits toward liver damage from cinchophen, as contrasted with that of dogs, might be explained on the basis of the relative carbohydrate content of their food.

In the majority of instances, negative results were obtained in testing for urobilinogen with undiluted urine; with urine diluted 50 per cent with water, the results were always negative. The icterus index never gave values higher than 6. Readings were obtained by means of the DuBosc colorimeter or by the standard tube technic of Farahaugh and Medes.[7] We were surprised to find the urobilinogen test and icterus index giving no indication of the change found as a routine in the liver following the administration of cinchophen.

While this work was in progress, Churchill and Van Wagoner[8] reported on an experimental study of acute cinchophen poisoning in dogs given large (twenty-seven times the calculated therapeutic dose) amounts of cinchophen. Ulcers were found in the mucosa of the

6. Graham, E. A.: The Resistance of Pups to Late Chloroform Poisoning in Its Relation to Liver Glycogen, J. Exper. Med. **21**:185, 1915.

7. Farahaugh, C. C., and Medes, G.: A New Set of Potassium Dichromate Standards for Determination of the Icterus Index, J. Lab. & Clin. Med. **14**:681, 1928-1929.

8. Churchill, T. P., and Van Wagoner, F. H.: Cinchophen Poisoning, Proc. Soc. Exper. Biol. & Med. **28**:581 (March) 1931.

stomach and lesions in the liver, which varied from "small areas of coagulation necrosis" to "complete disappearance of liver cells in small areas." The gastric and intestinal mucosa of the rabbits and of one dog, which were killed without waiting for recovery observations, were found to be without evidence of ulceration or even inflammation. The difference in the doses used in the two studies may well account for the presence or absence of damage produced in the mucosa of the upper alimentary tract.

CONCLUSIONS

1. Cinchophen apparently produces damage to the cells of the liver in dogs and rabbits following the administration of that drug by mouth for short periods of time.

2. The degree of liver damage varies directly with the dosage of cinchophen.

3. Dogs appear to be more susceptible to cinchophen toxicity than rabbits.

4. The icterus index and urobilinogen test do not indicate the extent of liver damage in the dog and rabbit that is evident on histologic examination.

5. The therapeutic employment of cinchophen does not seem justifiable in view of the evidences of its toxicity.

ABSORPTION OF COMPOUND SOLUTION OF IODINE FROM THE GASTRO-INTESTINAL TRACT

WITH SPECIAL REFERENCE TO THE ABSORPTION OF FREE IODINE

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Although iodine had been used with beneficial results in isolated cases of exophthalmic goiter prior to 1923, the widespread use of compound solution of iodine, U.S.P., is the result of a paper by Plummer and Boothby [1] published in that year. Since then compound solution of iodine has been used by nearly every clinician for treatment and in the preoperative and postoperative care of patients with this disease. Plummer and Boothby [1] stated that they used liquor iodi compositus "because it is an aqueous solution of iodine (5 per cent) and potassium iodide (10 per cent) and therefore provides a large amount of iodide loosely combined with potassium."

It would appear that Plummer and Boothby [1] believed that since compound solution of iodine contains free iodine, a greater amount of iodine is available for absorption than there would be if potassium iodide were used alone. Although many papers on the clinical results of the administration of compound solution of iodine have accumulated, a careful survey of the literature has failed to reveal any experimental data on the absorption of this solution.

This study was originally begun to ascertain whether or not iodine in the form of compound solution of iodine was absorbed from the large bowel. Its scope was subsequently widened so that studies have been made of the absorption of free iodine, of iodine in compound solution of iodine, of potassium iodide and potassium iodate from the large bowel of the dog. Studies were then made of the absorption of free iodine, of iodine in compound solution of iodine and of iodide from the stomach and small intestine. It was necessary to concern ourselves with the form in which iodine is absorbed from the gastro-intestinal tract and the rate of absorption when iodine in different forms is used.

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1. Plummer, H. S., and Boothby, W. M.: The Value of Iodin in Exophthalmic Goiter, Collected Papers of the Mayo Clinic and the Mayo Foundation, 1923, vol. 15, p. 565.

METHOD

Normal healthy dogs were used in all experiments. Sodium iso-amyl-ethyl barbiturate (sodium amytal) was the anesthetic used in each instance, being administered intraperitoneally in a dosage of 50 mg. per kilogram of body weight. Each experiment covered a period of two hours.

Isolation of the Colon.—A midline incision was made through the skin, fasciae and linea alba. The ileocecal region was then isolated, and the ileum ligated as close to the cecum as possible with a heavy ligature. The appendix was dissected free from its mesenteric attachment for a short distance and the tip cut off. A Paul tube fitted on each end with a small piece of rubber tubing was then carefully inserted into the appendix, and care was taken that the tube extended into the colon. The tube was made secure and watertight by double ligation with heavy ligatures. A funnel was attached to the rubber tubing of the Paul tube, and the colon thoroughly cleansed with warm tap water until the water returned perfectly clear. Two purse string sutures of strong linen thread were sewed around the anus, and then a Paul tube was inserted well into the rectum. The purse strings were then tightened. The colon was again rinsed in order to ascertain whether or not any water leaked around the rectal tube. The colon was emptied by carefully forcing air through it. A clamp was then placed on the rubber tube attached to the rectal Paul tube, and the solution to be studied was allowed to run into the colon from the appendical tube at a pressure of not over 100 mm. of water, until the colon was moderately distended. A clamp was then placed on the rubber tube attached to the appendical Paul tube. The wound was held together by two or more Allis forceps to conserve the body heat.

At the end of two hours the clamps were removed, and the solution was drained off by the means of air forced through the colon. The dog was killed immediately, and the entire colon, excluding the portion from the internal sphincter to the anus, was removed for the analysis of its iodine content by fusing the intestine with sodium hydroxide and sodium nitrate.

Isolation of the Small Intestine.—The operation performed on the small intestine was similar to that on the colon. The portion of the intestine selected for investigation was isolated, and a Paul tube was inserted in each end. The bowel was cleansed as previously described, and the standard solution was introduced under similar precautions. The jejunum and ileum were the portions studied. The sections used were later removed and fused as previously described.

Isolation of the Stomach.—When the stomach was being studied, the procedure was to ligate the duodenum about 1 inch (2.5 cm.) from the pyloric sphincter. An opening was then made in the duodenum, and the rubber was attached to a Paul tube inserted through the sphincter into the stomach. Double ligatures held the tube firmly in place. A stomach tube was inserted through the esophagus, which was then ligated at the cardiac orifice to the stomach. After the stomach was thoroughly cleansed and emptied, the standard solution was introduced. Care was taken not to overdistend the viscus. On removing the solution to be studied, it was deemed sufficient to wash the stomach with approximately 1,000 cc. of distilled water and analyze the washings rather than to fuse the organ and analyze the fused material.

The method employed for the determination of total iodine was that devised by Kendall,[2] with the exception of the slight modifications suggested by Kelly and

2. Kendall, E. C.: Determination of Iodine in Connection with Studies in Thyroid Activity, J. Biol. Chem. **43**:149, 1920.

Husband.[3] The sodium bisulphite was prepared by passing sulphur dioxide through a solution containing an excess of sodium bicarbonate. Blanks were run at frequent intervals in order to determine that the reagents used were iodine-free. The determination of the amount of free iodine in the solutions introduced was accomplished by the addition of starch solution [4] and titration with thiosulphate. All determinations were made in triplicate.

The compound solution of iodine used in the experiments on the colon was freshly prepared after the method described in the "United States Pharmacopeia." In all experiments in which this solution was used, 1 cc. was diluted with 99 cc. of distilled water.

The aqueous solution of free iodine was prepared by gently heating iodine crystals in distilled water until a deep brown color resulted. The solution was then filtered. In animal 864, the standard solution was made by triturating a small amount of potassium iodine with a large excess of crystalline iodine and a few drops of distilled water. The paste thus formed was then diluted with distilled water and filtered.

TABLE 1.—*Absorption of a Diluted Compound Solution of Iodine from the Colon*

			Solution Introduced				Solution Recovered			Intestinal Wall			Total Iodine Lost	
Dog	Weight, Kg.	Sex	Volume, Cc.	Total Iodine, Mg.	Free Iodine, Mg.	Free Iodine, per Cent	Volume, Cc. per Cent	Total Iodine, Mg.	Volume Change, Cc.	Weight, Gm.	Length, Cm.	Iodine Content, Mg.	Mg.	Per Cent
860	11.9	♀	110	96	..	..	79	43	31	88	35	4.4	49	51
1085	11.6	♂	140	124	50	41	114	66	26	53	30	2.5	55	44
1087	12.7	♀	182	156	75	48	94	62	88	66	34	2.8	92	59
1105	11.7	♂	204	167	81	49	167	111	37	52	35	1.3	55	33
1116	13.3	♀	176	93	39	42	97	39	79	64	28	2.2	51	55
Average														48.4
Probable error														±4.6

In this study no attempt was made to make determinations of the iodine in the blood.

RESULTS

Colon.—Table 1 gives the results of five experiments in which a diluted compound solution of iodine was placed in the colon. The absorption of iodine varied from 33 to 59 per cent, the average being 48.4 ± 4.6 per cent.

In these experiments I was unable, at any time, to elicit a blue color on the addition of starch solution to the fluid recovered from the colon at the completion of the experiment; this indicates that after a two-hour period in the colon no free iodine was present. The free iodine might have formed some chemical combination or have been adsorbed

3. Kelly, F. C., and Husband, A. D.: Method of Estimating Minute Quantities of Iodin in Biological Material, Biochem. J. **18**:951, 1924.

4. Treadwell, F. P., and Hall, W. T.: Quantitative Analysis, New York, John Wiley & Sons, Inc., 1924, vol. 2, p. 557.

to protein, mucus or fat. In order to ascertain what became of the free iodine present in the diluted compound solution of iodine, a new series of experiments was performed.

If the free iodine were adsorbed to the fat, mucus or proteins of the intestinal tract, a pink color would have been obtained when some of the recovered solution was thoroughly shaken with chloroform or a blue color when starch was added. This was tried, but the results were negative.

In the second group of experiments (table 2, group 1), solutions containing from 98 to 100 per cent of free iodine were introduced into

TABLE 2.—*Experiments Made to Ascertain What Becomes of Free Iodine Present in Diluted Compound Solution of Iodine*

			Solution Introduced			Solution Recovered			Total Iodine Lost	
Drug	Locus	Dog	Volume, Cc.	Total Iodine, Mg.	Free Iodine, Mg.	Volume, Cc.	Total Iodine, Mg.	Intestinal Wall Iodine Content, Mg.	Mg.	Per Cent
1. Aqueous iodine	Colon	864	129	35	35	88	21	1	14	38
		968	126	55	55	65	19	2	34	62
2. Potassium iodide	Colon	724	148	75	..	80	27	1	47	63
		1091	198	97	..	111	37	1	60	62
3. Iodate	Colon	1090	155	62	..	90	41	1	20	32
4. Compound solution of iodine	Ileum	1126	64	62	26	26	16	1	45	73
		812	40	40	18	25	13	1	26	64
5. Aqueous iodine	Ileum	1115	160	46	46	94	14	1	31	67
		1147	61	18	18	16	3	1	14	77
		1148	162	50	50	121	18	1	31	62
6. Potassium iodide	Ileum	553	80	32	..	34	7	1	24	74
		513	47	22	..	13	3	1	18	80
7. Compound solution of iodine	Jejunum	1126	56	54	23	34	15	1	39	72
		812	69	68	31	21	14	2	52	76
8. Aqueous iodine	Jejunum	968	71	31	31	23	5	1	25	81
		1147	55	16	16	7	2	1	14	84
		1148	123	38	38	59	10	1	27	72
9. Potassium iodide	Jejunum	553	85	34	..	47	6	1	27	80
		513	66	31	..	16	6	1	24	78

the colon. Tests for starch and chloroform were performed, with negative results for the recovered solutions, indicating that the free iodine had been changed.

The addition of sufficient dilute hydrochloric acid to bring a solution, containing iodine and iodate, to a p_H of about 6.4, with starch as an indicator, will give a blue color. I have been successful in only a few instances in obtaining positive tests for the presence of both iodate and iodide in the recovered solutions. The addition of iodate and dilute hydrochloric acid to the recovered solutions, whether diluted compound solution of iodine or an aqueous solution of free iodine had been used, elicited a blue color with a starch indicator. This indicated that iodide was present.

In table 2 (group 2) are given the results of the absorption of a solution of potassium iodide from the colon, the concentration of iodine being approximately the same as that of the free iodine in the experiments in which a diluted compound solution of iodine was used. It will be noted that the absorption of iodine, in the form of potassium iodide, was higher than that found when diluted compound solution of iodine or an aqueous solution of iodine was used. However, there were considerable variations in the percentile absorption in the individual experiments.

One experiment (group 3, table 2) was performed with a solution of potassium iodate that had an iodine concentration approximately the same as that used in our other experiments, in order to ascertain the rate of absorption and to determine whether or not the iodate was reduced to the iodide. The absorption of iodine was 32 per cent. The addition of starch and dilute hydrochloric acid to the original solution failed to produce a blue color, but the addition of these substances to

TABLE 3.—*Iodine Content of Normal Intestinal Wall: Control Experiments*

	Weight, Gm.	Length, Cm.	Total Iodine Content
Colon	58.69	30.00	0.31
Colon	54.38	28.75	0.45
Small intestine	78.00	87.50	0.10
Small intestine	90.00	150.00	0.19

the recovered solution produced a blue color. This indicated that iodide was now present.

Similar experiments, with the exception of the one performed with iodate solution, were carried out on the ileum, jejunum and stomach. The results will be presented in the order of the viscus named.

Ileum.—Group 4, table 2, gives the results of two experiments in which a dilute compound solution of iodine was introduced into the ileum. The absorption was 65 to 73 per cent. Tests for free iodine in the recovered solution were negative. When an aqueous solution of free iodine was placed in the ileum (group 5), the absorption was 62 to 77 per cent, and with potassium iodide alone (group 6), from 74 to 80 per cent.

Jejunum.—The results of the absorption from the jejunum of diluted compound solution of iodine, an aqueous solution of iodine and a solution of potassium iodide are given in table 2, groups 7 to 9. The figures obtained in the individual experiments indicate that the amount of iodine absorbed from these solutions is practically the same.

Stomach.—A series of seven experiments was performed on the stomach. These experiments were more difficult to control from the standpoint of complete emptying of the gastric washings. The con-

version of free iodine into iodide and iodate does not take place in an acid medium. The repeated washing of the stomach reduces the amount of acid in the later washings to a minimum, and under such conditions it has been found that free iodine can be changed to iodide. In this type of preparation, 18 per cent of the solution of free iodine in water was absorbed; 27 per cent of iodine was absorbed from a diluted compound solution of iodine and 31 per cent of the iodine from a solution of potassium iodide. In every instance the recovered solutions gave negative reactions for free iodine, but positive tests for iodide.

Iodine Content of Normal Intestine.—Two normal colons and two portions of normal intestine were individually fused and their iodine content analyzed by Kendall's method.[2] This was done to serve as a control for other experiments. The total iodine content in milligrams for the normal colon (average 0.38) and normal small intestine (average 0.14), table 3, was so small as to be considered negligible, in comparison with the final results in our experiments.

Time Required for the Conversion of Free Iodine Into Iodide.—That not more than two hours are required for the complete conversion of free iodine, in the concentrations used in these experiments, was indicated by the fact that negative reactions for starch and chloroform were obtained in each instance on the solutions recovered from the gastro-intestinal tract. It was thought that it would be interesting to ascertain the minimum time required for the reaction to be completed. When an aqueous solution of free iodine was introduced into 200 cm. of small intestine, prepared in the usual manner, I was unable to elicit a blue color with starch four minutes after the solution had been introduced. The addition of dilute hydrochloric acid and starch gave a blue color indicating the presence of both iodide and iodate.

COMMENT

The data obtained from these experiments indicate that free iodine, when introduced into the gastro-intestinal tract, is converted into iodide. We attribute this phenomenon to an inorganic reaction.

Free iodine will combine with sodium bicarbonate in vitro as follows: $6NaHCO_3 + 3I_2 = 5NaI + NaIO_3 + 6CO_2 + 3H_2O$. This reaction can be made to take place at will, by passing iodine vapor through a saturated solution of sodium bicarbonate. Before the solution is tested with dilute hydrochloric acid and starch for the presence of iodide and iodate, the free iodine must be entirely driven off by boiling. That this reaction takes place in the range of alkalinity present in the intestinal tract seems evident.

Our experimental data indicate that free iodine is converted into iodide when instilled into the gastro-intestinal tract. If this is true,

the administration of potassium iodide in the treatment for exophthalmic goiter should be of the same value as compound solution of iodine. Neisser,[5] Loewy and Zondek[6] and recently Lerman and Means[7] have shown that potassium iodide is as efficacious as compound solution of iodine in controlling the basal rate in hyperthyroidism. Lerman and Means[7] suggested that "potassium iodide solution is preferable to Lugol's solution . . . being equally effective and less offensive to take." Judging from these authors' clinical data and the experimental data on which this paper is based, I am in full accord with such a statement.

As previously stated, Plummer and Boothby[1] used compound solution of iodine, because it "provides a large amount of iodine loosely combined with potassium," assuming that more iodine would be present for absorption. The studies here reported do not bear out this assumption.

CONCLUSION

Studies on the rate of absorption of free iodine in aqueous solution, of a diluted compound solution of iodine and of potassium iodide and potassium iodate from the gastro-intestinal tract of the dog are reported. These studies show that the iodine is converted to iodide before it is absorbed. If these studies are applicable to the human being, they would seem to refute the assertion that compound solution of iodine is more beneficial than potassium or sodium iodide in controlling the high basal metabolism of exophthalmic goiter, since when compound solution of iodine is used, the percentage of iodine absorption is no greater than when potassium or sodium iodide is administered.

Dr. C. G. Johnston and Dr. I. S. Ravdin gave assistance and advice in this study.

5. Neisser, E.: Ueber Jodbehandlung bei Thyreotoxikose, Berl. klin. Wchnschr. **57**:461, 1920.

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7. Lerman, J., and Means, J. H.: Iodin in Exophthalmic Goiter: A Comparison of the Effect of Ethyl Iodid and Potassium Iodid with that of Lugol's Solution, Am. J. M. Sc. **181**:745, 1931.

IMMUNITY TO TUBERCULOSIS

RELATION OF CUTANEOUS ALLERGY AND RESISTANCE TO TUBERCULOUS INFECTION FOLLOWING VACCINATION WITH B C G

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My observations [1] that student nurses with positive reactions to the Pirquet test present greater resistance to tuberculous infection than those whose reaction is negative, suggest the importance of cutaneous allergy in relation to immunity in tuberculosis. I have also demonstrated that the subcutaneous or intracutaneous injection of B C G vaccine, in nurses presenting negative reactions to the test, is able to produce a positive reaction within a certain time. On this account I was led to believe that vaccination with B C G exercises a protective influence against tuberculous infection. These conclusions made in 1926 are the basis for the decision to vaccinate subcutaneously with B C G the student nurses in the Oslo Kommunale Sykehus who enter on their course with negative reactions to the Pirquet test. This method of vaccination has been followed systematically in this hospital since January, 1927.

Among the approximately 120 student nurses admitted annually to this hospital, nearly 50 per cent give negative reactions to the Pirquet test. During the three year course of instruction the nurses are thoroughly exposed to tuberculous infection in caring from time to time for from 300 to 400 tuberculous patients. This fact has been adequately stressed in my previous publications.[1]

The conditions for intimate observation and study of the general health of these student nurses are ideal. Since tuberculous infection most often manifests its eventual malignant course for a short time after the infection, there is now sufficient reason to analyze carefully the direct results of vaccination during the past five years. What conclusions can be drawn from these experiences?

In table 1 is summarized the incidence of tuberculous diseases among he persons vaccinated with B C G strain and those not vaccinated up to

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From the Medical Division, Ullevål Kommunale, Sykehus.

1. Heimbeck, J.: Om tuberkuloseresistens, Norsk mag. f. lægevidensk. **88**: 457, 1927. Cutiréaction de Pirquet après la vaccination par B C G, Presse méd. **38**:1070, 1927; Immunity to Tuberculosis, Arch. Int. Med. **41**:336 (March) 1928; Tuberkulose Infektion und Tuberkulose Vakzination, Ztschr. f. Tuberk. **52**:378, 1928; Tuberculous Infection, Arch. Int. Med. **47**:901 (June) 1931.

July 31, 1931. It is observed that the Pirquet reaction and immunity against tuberculous infection are reciprocally related. Thus there were among 454 persons with positive reactions to the Pirquet test twelve cases of tuberculosis, or 2.6 per cent, while among 253 subjects with negative reactions there were seventy-five cases of tuberculosis, or 29.6 per cent. The annual curves have been uniform with these figures.

It is evident, however, that the results for each year have not been uniform among the vaccinated persons. These subjects seem to fall into

TABLE 1.—*Relation of Cutaneous Allergy and the Incidence of Tuberculous Infection Among Student Nurses During Their Hospital Service*

Year	Number of Student Nurses	Pirquet Test	Vaccinated with BCG	Number Taken Ill with Tuberculosis									
				During Half Year								Later Half Year	Total
				1	2	3	4	5	6	7	8		
1924	58	Positive	—	—	—	—	—	—	—	—	—	1	1
	51	Negative	—	5	4	1	4	1	1	1	—	—	17
1925	42	Positive	—	—	—	—	1	—	—	—	—	—	1
	72	Negative	—	8	4	6	2	—	1	—	—	—	21
1926	52	Positive	—	1	—	—	—	—	—	—	—	—	1
	62	Negative	—	8	4	2	—	2	—	—	—	—	16
1927	64	Positive	—	—	1	1	—	—	—	—	—	—	2
	12	Negative	—	4	—	1	—	—	—	—	—	—	5
	45	—	45	—	—	—	—	1	—	—	—	..	1
1928	65	Positive	—	1	—	2	—	1	—	..	..	..	4
	19	Negative	—	5	4	1	—	—	1	..	..	..	11
	40	—	40	1	—	1	—	1	—	..	..	..	2
1929	61	Positive	—	2	—	—	—	1	..	..	..	..	3
	4	Negative	—	—	—	—	—	—	..	..	..	..	0
	52	—	52	—	1	1	—	—	..	..	..	..	2
1930	58	Positive	—	—	—	—	..	..	..	..	..	..	0
	7	Negative	—	1	3	—	..	..	..	..	..	..	4
	43	—	43	—	8	1	1	..	..	..	..	..	10
1931	54	Positive	—	—	..	..	..	..	..	..	..	..	0
	26	Negative	—	1	..	..	..	..	..	..	..	..	1
	27	—	27	3	1	..	..	..	..	..	..	..	4

Summary: Positive Pirquet tests: 454; tuberculosis: 12 (2.6 per cent).
Negative Pirquet tests: 253; tuberculosis: 75 (29.6 per cent).
Vaccinated with BCG: 207; tuberculosis: 20 (9.6 per cent).

two groups: First, those vaccinated during the years 1927, 1928 and 1929, and second, those vaccinated during 1930 and 1931. In the first group, six cases of tuberculosis occurred among 137 vaccinated persons. The period of observation extended from two years to four years and a half. In the second group, there were fourteen cases of tuberculosis among seventy vaccinated persons, the longest period of observation being one year and a half. These results require a closer scrutiny in order to evaluate the effects of vaccination and of other attendant circumstances.

I have previously called attention to the great variableness in local and allergic reactions following vaccination with B C G. While in cer-

tain persons local reactions develop at the site of inoculation, others fail to react, and in some the reaction to the Pirquet test becomes positive following vaccination, while in others it remains negative. These variable results are shown in table 2.

A total of 207 vaccinations have been made. Forty of these must be eliminated (groups 7 and 8) from the final appraisal because of inadequate controls, and the last three, performed on July 10, 1931, must also be eliminated because the general incubation time for B C G has not yet expired at the time of this report. This leaves 164 vaccinations for consideration in the present study. When the subjects are grouped according to their reactions to the Pirquet test following vaccination and

TABLE 2.—*Local and Allergic Reactions Following Vaccination with BCG*

Vaccinations		Grouping of Reactions								
Year	Number	P+,* Inf. 2 Mm. or More	P+, Inf. Under 2 Mm.	P+ and Local Inf.	P+ and Local Abscess	P− and Local Inf.	P− for 6 Months or Until Infection	Not Controlled First 6 Months	Course Discontinued	Ill.
		1	2	3	4	5	6	7	8	
1927	45	23	6	8 1	2	..	1	4	1	1
1928	40	12	6 1	6	..	2	10 1	2 1	2	3
1929	52	11	3 1	5	2	12	2 1	24	4	2
1930	43	5	..	..	1	..	30 10§	..	1	10
1931	27†	1	1	1	11	32 1	5 3	..	2	4

* In this and the following table, P+ represents positive Pirquet reaction; P−, negative Pirquet reaction; Inf. indicates infiltration.

† The last three vaccinated persons (July 10, 1931) are not included.

‡ Infiltration not larger than a pea.

§ One of these subjects died of tuberculous meningitis.

before they were exposed to tuberculous patients, the following results are obtained: In 104 persons the Pirquet test became positive (groups 1, 2, 3 and 4) and in sixty persons the reaction remained negative (groups 5 and 6). Among the 104 subjects with positive reactions to the Pirquet test, tuberculosis developed in three or 3 per cent, while among the sixty with negative reactions, tuberculosis developed in sixteen, or 26.6 per cent. These results are not surprising according to the present interpretation of the Pirquet reaction. This criterion furnished the chief reason for the systematic vaccination with B C G of persons with negative reactions to the Pirquet test, since it appeared that these persons are exquisitely susceptible to tuberculous infection. Subsequently, the course adopted by my associates and me has been to produce a positive reaction to the Pirquet test by means of the subcutaneous injection of the B C G vaccine.

The significance of the Pirquet test is further enhanced when the persons with doubtful reactions (group 2) who present an area of inhibition measuring less than 2 mm. in diameter are eliminated. Among these subjects with doubtful reactions sixteen persons are listed, and in two of these tuberculosis developed. This group is sharply separated from the groups 1, 3 and 4, which present distinct reactions to the Pirquet test, in which the area of infiltration is in excess of 2 mm. in diameter. Only a single case of tuberculosis occurred among the eighty-eight persons with distinctly positive reactions to the Pirquet test. So group 2 stands between the positive and the negative groups (groups 5 and 6) which presented sixteen cases of tuberculosis among sixty persons.

It is quite apparent, therefore, that it is the vaccination with B C G, that elicits the positive reactions to the Pirquet test which really produces an effective resistance against tuberculous infection. Should cutaneous allergy fail to be developed following the vaccination with B C G there is good reason to conclude that no effective vaccination has been produced against tuberculous infection. The many divergent results reported following vaccination with B C G must be attributed to the failure of the vaccine to call forth cutaneous allergy. While certain persons have become allergized and immunized following vaccination with B C G, in others it has not been effective. And since only occasional studies have been made of the reaction to tuberculin of persons vaccinated with B C G, one is not in a position to know positively the allergizing effect of the vaccination, that is, the number of persons successfully vaccinated.

Table 2 shows clearly the variableness of the local and allergic manifestations following vaccination with B C G. Certain injections elicit local abscess and allergy; others produce no reactions, while still others result in intermediary manifestations.

During the year 1927, a dose of 0.05 mg. of B C G was administered to each of forty-five persons. Ten had local reactions, of which two were abscesses, while thirty-five showed no local reaction; in one the reaction remained entirely negative, locally and allergically, following vaccination.

These variations may be conditioned by two factors: (1) the person treated with B C G and (2) the injected vaccine. The ability to react to B C G vaccine must doubtless show wide variations. Although they are treated on the same day and with the identical bacterial emulsion and dosage, the effects are most variable in a group of persons. For example, on Jan. 11, 1928, nineteen student nurses with negative reactions to the Pirquet test were vaccinated with 0.05 mg. of B C G. One of these nurses was eliminated because of lack of control. In the

remaining group of eighteen, local infiltration developed in five, while in the other thirteen the reaction remained negative locally. When tested with tuberculin, ten gave positive reactions to the Pirquet test following vaccination (table 3, groups 1, 2 and 3), and in eight the Pirquet test remained negative (groups 5 and 6). Similar variations have been repeatedly observed and seem quite natural.

Concerning the second factor, the vaccine employed, a certain variableness is encountered here also, which is best illustrated by the following observations (table 3): On Feb. 25 and 28, 1927, five student nurses were given injections of 0.05 mg. One subject should be eliminated because of lack of control. In the remaining four the Pirquet test became positive, and in one an abscess developed locally. On July 14, of the same year, twenty-one student nurses received the

TABLE 3.—*The Variability of the Effectiveness of Vaccination with BCG*

	Grouping of Reactions							
Date, Number and Dose of Vaccine	P +, Inf. 2 Mm. or More	P +, Inf. Under 2 Mm.	P + and Local Inf.	P + and Local Abscess	P — and Local Inf.	P — for 6 Months or Until Infection	Not Controlled 6 Months	First Course Discontinued
Group	1	2	3	4	5	6	7	8
2/25-28/27..... 5 vaccinated, 0.05 mg.	3	..	..	1	..	..	1	..
7/14/27..... 21 vaccinated, 0.05 mg.	14	1	1	..	..	1	3	1
1/11/28..... 19 vaccinated, 0.05 mg.	4	2	4	.	1	7	1	..
6/14/29..... 10 vaccinated, 0.025 mg.	1	2	5	1	..	1	..	..

same dose (0.05 mg.) of B C G. Four of these should be eliminated. Among the remaining seventeen nurses vaccinated a local infiltration developed in one, the Pirquet test became positive in fifteen and there was a doubtful reaction to tuberculin in one, and in one the reaction to the Pirquet test remained negative. The effectiveness of these two vaccinations was accordingly practically uniform. But the results of the vaccination on Jan 11, 1928, were not so, as was mentioned. Among the nineteen nurses vaccinated local infiltration developed in five, but still the reaction remained negative in eight, and in two the reaction to the Pirquet test was doubtful. On June 14, 1929, the vaccine was again more effective. On that day only 0.025 mg. of B C G was injected into ten student nurses. In five local infiltration developed, in one case a local abscess; in seven the reaction to the Pirquet test became positive, while two reactions were doubtful (group 2), and only one remained negative.

A comparison of the results compiled during the entire year of 1929 with those obtained for 1930 also discloses a marked variability in the

effects of vaccination with B C G. Fifty-two persons were vaccinated during 1929; fifty of these received 0.025 mg. and two received 0.03 mg. of B C G. Table 2 shows that among the twenty-four who were adequately controlled, in eighteen the Pirquet test became positive, in seven local reactions developed, and in two tuberculosis developed as a result of a later infection. During 1930, forty-three persons were vaccinated. Of these, twenty-eight received 0.03 mg., fourteen received 0.025 mg. and one was given 0.04 mg.—in general, greater doses than in 1929. But among the forty-two persons vaccinated who were exactly controlled, in only one did a local reaction (an abscess) develop, and in only six did the Pirquet test become positive, while in thirty-six it remained negative. In ten members of this group tuberculosis developed when the nurses later were exposed to infection.

The B C G vaccine employed in these different groups appears, therefore, to yield a variable local and allergic effect. These different effects of the B C G vaccinations are remarkable.

It is possible that the age of the B C G vaccine may play an important rôle. This seems to be suggested in the following observation: On June 11, 1930, ten student nurses were given injections of 0.03 mg. of B C G. Since this culture had grown poorly, it became necessary to leave it in an incubator for forty-five days before sufficient growth had taken place for it to be used as a vaccine. Among the ten nurses vaccinated with this lot, none showed local irritation, and in all of them the Pirquet test remained negative as before vaccination. In five of these persons tuberculosis has since developed. The vaccine seems, therefore, to have failed to produce any immunizing effect. It is only in this instance that the age or dysgonic property of the B C G strain seems to have been responsible for its ineffectiveness as a vaccine. The production of vaccine has otherwise always been according to the directions of Calmette. But the possibility of uncontrollable variations in the mediums employed for the cultivation of B C G and in the production of the vaccine must also be taken into consideration. Whatever is the real explanation of these divergent results, one thing is certain, namely, that the B C G vaccine is not constant in eliciting local and allergic effects. The B C G virus cannot be considered as a fixed virus in an absolute sense, i. e., also in its immunizing properties, although the strain remains avirulent. It is imperative that the strain should produce cutaneous allergy in order to insure against tuberculous infection. A positive reaction to the Pirquet test, or similar tuberculin tests, should be elicited following subcutaneous vaccination with B C G. This remains a potent criterion of the fact that the vaccinated person is immunized against tuberculous infection.

CONCLUSIONS

The susceptibility to tuberculous infection among student nurses with negative reactions to the Pirquet test who are exposed to tuberculous patients is excessively high (29.6 per cent), in contrast with a relatively high resistance to tuberculous infection among student nurses with a positive reaction to the Pirquet test (2.6 per cent).

Subcutaneous injection of the B C G vaccine is capable of converting a negative reaction to the Pirquet test to a positive reaction, with subsequent marked increase in resistance to tuberculous infection.

The absence of a positive reaction to the Pirquet test following vaccination with B C G must be considered as an indication of inadequate vaccination and of the fact that the vaccinated person's liability to tuberculous infection has remained practically unaltered, and revaccination should be done.

PROLONGED USE OF MASSIVE DOSES OF UREA IN CARDIAC DROPSY

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This report presents some of our results of the prolonged use of large amounts of urea in cases of cardiac dropsy. We shall emphasize, among other matters, chiefly three points; first, that the diuretic properties of this drug do not weaken during months and several years of practically uninterrupted use; second, that there follow no demonstrable deleterious effects on the patient; more specifically, the renal structures remain unaltered and their function unimpaired, and third, that urea acts, alone or in combination with other agents, in selected cases, as an excellent prophylactic in preventing the reaccumulation of edema. Of the many patients in our wards who were subjected to treatment with urea, we are reporting at this time the cases of five in full. These cases will illustrate the methods and results.

METHODS

Nearly all the patients in this study have been at the Montefiore Hospital for many months or several years; some have had several previous admissions. The majority, on admission, presented signs of advanced congestive heart failure with marked anasarca; they suffered from either chronic rheumatic or arteriosclerotic and hypertensive cardiac disease, but all but one were free from renal complications.

The type of diet given the patients varied: Some took the regular house diet, containing at least from 5 to 6 Gm. of sodium chloride per day; others took a salt-poor diet, containing about 2 or 3 Gm. of sodium chloride. The patients lived sometimes on one and sometimes on the other diet over various periods. Several received, in addition, digitalis, mersalyl or other diurectics. These details are noted elsewhere.

As a rule, except during the first few days immediately after admission, no attempts were made to limit the intake of fluid. There is no

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From the Medical Division of Montefiore Hospital, Dr. B. S. Oppenheimer, Director.

† Stroock Fellow for 1930.

doubt that large doses of urea greatly increase the patient's thirst, and he proceeds to drink much larger volumes of water. It proved, however, impracticable to limit the patients' intake of water in a large ward service, because surreptitiously they drink water copiously. More reliable guides to the patient's progress with regard to loss or gain in edema were: first and most important, his body weight, which was particularly valuable since the caloric intake was ample (at least 2,000 calories per day) to prevent a loss in flesh, and second, the measurement of the daily urinary output,[1] which was not always accurate, as already mentioned, but which was valuable, nevertheless, as a reflection of how the normal channels of excretion were working.

The doses of urea varied between 10 and 25 Gm., two or three times a day in 40 per cent water solution. Whenever possible, at the beginning of treatment the patients received about 18 Gm. three times a day. It was seldom necessary to give more than this amount, although in some cases as much as 27 Gm. three times a day was administered. After satisfactory diuresis, the drug was gradually reduced, the patients receiving 15 or even 12 Gm. three times a day, and in some instances the patient remained on a 12 Gm. dose twice daily, especially when the drug was employed to function as a "chronic" prophylactic measure to prevent the reaccumulation of edema.

As a general rule, the patients took the drug without remonstrance, although its taste is very unpleasant. We administered it as a 40 per cent [2] aqueous solution, adding no sugar. In private practice we have added the juice of a pressed lemon, or else we have used as a vehicle from 100 to 200 cc. of beer or uncooked tomato juice. Recently we have tried using fresh pineapple juice or raspberry syrup, mixing from 50 to 90 cc. of syrup with an equal quantity of water as a diluent for each single dose of urea. The syrups seems to be agreeable vehicles. There were seldom any untoward effects, such as nausea, heart burn

1. There are, of course, important factors in the total loss of fluid, as exemplified by the extrarenal output of water, such as "insensible perspiration," but these were not studied by us. For references see: Veil, W. H.: Deutsches Arch. f. klin. Med. **119**:376, 1916. Benedict, F. G., and Root, H. F.: Insensible Perspiration: Its Relation to Human Physiology and Pathology, Arch. Int. Med. **38**:1 (July) 1926.

2. Only recently our attention was directed to the fact that patients in the hospital were receiving their urea in a 40 per cent solution and not in a 50 per cent solution as charted. This raised the doubt in our minds that, perhaps, the doses taken by the patients studied in this report may have been actually one-fifth less than we had believed. Although we think that our patients may have taken the full amounts, for example, from 70 to 80 Gm. daily, we deemed it more accurate and safer to base our results on a corrected calculation. Accordingly, all figures noted in the text represent four fifths of the amount charted in the history records.

or other gastric symptoms. We tried producing a chocolate or gelatin covered tablet, but without success, because urea cannot be concentrated into tablets of small bulk for adequate dosage.

REPORT OF CASES

CASE 1.—R. Z., a woman, was admitted to the Montefiore Hospital six times, from 1923 to 1927, suffering from chronic rheumatic cardiovalvular disease. On Jan. 8, 1929, at the time of her last admission, she was 28 years old; she again showed congestive failure, auricular flutter and partial heart block, which changed to auricular fibrillation (she was taking digitalis). Toward the end of August of that year she grew worse, although she was receiving a maintenance dose of digitalis almost daily; on November 3, the therapy was supplemented with urea, from 24 to 36 Gm. daily. From September 1 until November 1 her weight was practically unchanged (from 133½ to 135 pounds [60.5 to 61.2 Kg.]). When she was given urea, however, for the next forty-five days, the weight fell to 122½

TABLE 1.—*Treatment and Results in Case 1*

Daily Grams of Urea	Admission Weight, Pounds	Days on Urea		Weight, Pounds	Other Diuretics
		1929			
0	133½	61	Sept. 1 to Nov. 1	135	Digitalis
24 to 36		45	Nov. 3 to Dec. 18	122½	Digitalis
		1930			
56		46	to Feb. 3	120	Digitalis
0		57	to April 1	125	Digitalis
36 (occas. 56)		82	to June 22	121	Digitalis
56		70	to Aug. 31	114 to 117½	Digitalis

pounds (55.5 Kg.) and the clinical condition improved. The dose of urea was raised to 56 Gm. through the next forty-six days, the weight touching 120 pounds (54.4 Kg.). The following fifty-seven days the patient took no urea, but she remained restored in cardiac efficiency and her weight did not rise above 125 pounds (56.7 Kg.). The next eighty-two days she took mostly 36 Gm. a day; the weight was 121 pounds (54. 9 Kg.). The final seventy days of this record she took 56 Gm. a day, and her weight fell to between 114 and 117½ pounds (51.7 and 53.3 Kg.).

This case demonstrates that digitalis alone was not able to restore the patient's cardiac efficiency and rid her of her signs of congestive failure, but that when urea, in doses of from 24 to 36 Gm. a day, was added, the desired result was achieved. Urea seemed very helpful in this case, although its administration was irregular because the patient refused the drug on several occasions. A point worthy of emphasis is that she finally required no other diuretics. Her renal function was good. She had an output of about 5.67 mg. of sodium chloride daily. The figures for the blood urea nitrogen were: 24.2 mg. per hundred cubic centimeters on Aug. 5, 1930, after urea had been withheld for the ten preceding days, and from 36.8 to 49 mg., while patient was receiving urea, thirteen and one-half months, and there was no disturbance in the urinary concentration power. She remained edema-free, although her cardiac reserve was very poor. She finally died of congestive heart failure, on July 1, 1931.

Case 2.—H. R., a man, aged 56, came to the Montefiore Hospital on Dec. 28, 1928. The diagnosis was degenerative cardiovascular disease, auricular fibrillation and congestive heart failure. He received digitalis practically daily until May 11, one hundred and twenty-eight days, during the initial nineteen days of which he took 56 Gm. of urea; his weight fell from 165½ to 148½ pounds (75 to 67.3 Kg.). The following twenty days, with 36 Gm. a day, the weight went still lower (134½ pounds [61 Kg.]); this figure was maintained over the next twenty-three days, with 56 Gm. daily. Urea was withheld for the next thirty-five days, and the weight rose to 141½ pounds (62 Kg.) and then dropped slightly (138½ pounds [62.8 Kg.]) with 56 Gm. daily until thirty-one days later, when the patient was discharged (May 11, 1929).

The patient returned the following year, on March 11, 1930, and again showed extreme heart failure with anasarca. This time he received no digitalis. His weight was 146 pounds (66.2 Kg.) on admission. During the first one hundred and fifty-six days he received 36 Gm. of urea daily and no mersalyl. His weight

Table 2.—*Treatment and Results in Case 2*

Daily Gm. of Urea	Admission Weight, Pounds	Days on Urea		Weight, Pounds	Digitalis	Mersalyl	Comment
56	166½	19	1929: Jan. 3 to Jan. 22	148½	2·4 cc. daily		
36	.....	20	to Feb. 11	134½	2·4 cc. daily	.....	Improved
56	.....	23	to Mar. 6	134¼	2·4 cc. daily		Feb. 21
0	.....	35	to Apr. 10	141½	2·4 cc. daily		
56	.....	31	to May 11	138½	2·4 cc. daily		
36	146	156	1930: Mar. 11 to Aug. 14	137	0		In July no
0	...	84	to Nov. 6	143	0	Nov. 7, 2 cc.	congestive
56	...	51	to Dec. 27	135 to 140	0	Dec. 13, 2 cc.	signs
36	141	13	1931: Jan. 1 to Jan. 13	142	0		
0	...	9	to Jan. 22	...	0	Jan. 21, 2 cc.	
56	...	9	to Feb. 1	...	0		
0	...	17	to Feb. 17	152	0		
56	...	11	to Feb. 28	142	0		

soon reached and remained at about 137 pounds (62.1 Kg.), and very early he exhibited marked clinical improvement, which he maintained. The following eighty-four days he took no urea; his weight stayed at about 143 pounds (64.9 Kg.), and he required but one injection of mersalyl. The final fifty-one days of this period he received 56 Gm. of urea daily and but one injection of mersalyl, and the weight varied from 135 to 140 pounds (61.2 to 63.5 Kg.). On December 27, he was discharged very much restored in cardiac efficiency and edema-free. This period, as well as the next period, represents a contrast interval wherein the patient took no digitalis, and urea was the mainstay of treatment.

Beginning Jan. 31, 1931, for thirteen days, the patient was given 36 Gm. of urea. The following nine days urea was withheld, but he received 2 cc. of mersalyl. The next nine days he took 56 Gm. of urea daily and again stopped for the next seventeen days so that by February 17, his weight had risen to 152 pounds (68.9 Kg.) as against 142 pounds (64.4 Kg.) on January 31. Fifty-six grams of urea daily reduced the weight to 142 pounds within eleven days.

It will thus be seen that in the third episode, reduction in the quantity of urea led to an increase in weight and to the appearance of mild signs of heart failure, and that this condition yielded rapidly to an adequate intake of urea. No digitalis was employed, and only one dose of mersalyl was given at the very beginning of this period.

The daily urinary output of salt of this patient was good, about 5.5 Gm., and covered his intake. On Aug. 1, 1930, his blood urea was 17.4 mg. per hundred cubic centimeters, urea having been stopped for three days; it was 26 mg. after he had been taking urea for ten and one-half months. The range of the specific gravity of the urine was normal. The renal function remained undisturbed.

Case 3.—When H. L., a man, aged 39, with hypertensive heart disease, entered the hospital on March 6, 1929, he had extreme heart failure and was water-logged. His auricles were not fibrillating. He was given digitalis daily, a dose of mersalyl intravenously on one occasion and thereafter 56 Gm. of urea daily. Within twenty-four days his weight declined from 164 to 147 pounds (74.4 to 66.7 Kg.), and his clinical condition improved markedly. During the next five hundred and eighty-two days he took 56 Gm. of urea daily and required in all but five injections of mersalyl (2 cc. each), widely spaced. The last months he took no digitalis. His output of salt in the urine was good; a concentration test of the urine showed normal renal function. On Aug. 1, 1930, his blood urea nitrogen was 18.6 mg. per hundred cubic centimeters of blood, three days after urea was discontinued; it varied from 30.1 to 36.6 mg. after twenty-three and one-half months of urea therapy. The elimination of urea in the urine was normal, about 4 per cent. During all this time the patient was practically edema-free and restored considerably in cardiac efficiency.

Table 3.—*Treatment and Results in Case 3*

Daily Grams of Urea	Admission Weight, Pounds	Days on Urea		Weight, Pounds	Mersalyl (2 Cc.)	Digitalis	Comment
			1929:				
56	164	24	March 15 to April 8	147	1929: March 21	2·4 cc. daily	
56		582	to Nov. 1, 1930	145	1930: Jan. 30, July 8, Aug. 6, Sept. 15, Oct. 24	Daily up to Dec. 1, 1929; daily from Aug. 14 to Sept. 30	Weight, 149½ pounds
		606 days					

This record also illustrates the futility of giving mersalyl when a residual edema-free weight is well established; thus, on Jan. 31, 1930, the patient's weight was 147¾ pounds (67 Kg.), and although he was not edematous, he received 2 cc. of mersalyl. The next day the weight stayed unchanged, and the following day it was 146 pounds (66.2 Kg.). A similar result was observed on July 8, 1930, when the weight was 145 pounds (65.8 Kg.); 2 cc. of mersalyl reduced the weight to 142 pounds (64.4 Kg.) the next day, and on the following day it was 143 pounds (64.9 Kg.).

Case 4.—When L. R., a man, aged 54, first appeared at the Montefiore Hospital on Sept. 17, 1927, he was known to have arteriosclerotic cardiovascular disease with hypertension and marked heart failure. Ten months later he went home much improved. On April 4, 1929, he returned; his heart failure was extreme. The blood pressure was 166 systolic and 90 diastolic, and there was pulsus alternans; electrocardiographic tracings disclosed premature ventricular beats but no auricular fibrillation. He received no digitalis, but was given during the initial twenty-six days four doses of mersalyl (2 cc. each) and 56 Gm. of urea daily. His weight fell from 175½ to 138 pounds (79.6 Kg. to 62.6 Kg.), and the clinical amelioration was striking. For the greater part of the next one hundred and eighty-four days he took 24 Gm. of urea daily, occasionally 36 Gm., and he required but two widely

spaced injections of mersalyl; the weight stayed at about 135 pounds (61.2 Kg.), and he was edema-free. An increase of urea to 56 Gm. daily for the following one hundred and eighty-one days lowered his weight to 127 pounds (57.6 Kg.), and he required but one injection of mersalyl during this time. For the next one hundred and twenty-two days, the daily dose of urea was 36 Gm., occasionally 56 Gm., but the patient required mersalyl somewhat more frequently, and his weight climbed to 138 pounds (62.6 Kg.), and continued to range between 132 and 140 pounds (59.9 and 63.5 Kg.) during the next two hundred and seventeen days, when he took 56 Gm. of urea daily.

This patient thus took large doses of urea practically uninterruptedly over seven hundred and thirty days. On Aug. 13, 1930, after having taken urea for more than one year, the blood urea nitrogen was only 15 mg. per hundred cubic centimeters, urea having been stopped for two days; after taking urea for twenty-one and one-half months, the blood urea nitrogen was 29.1 mg. The daily urinary

TABLE 4.—*Treatment and Results in Case 4*

Daily Grams of Urea	Admission Weight, Pounds	Days on Urea		Weight, Pounds	Mersalyl
56	175½	26	1929: April 4 to May 1	138	April 7, 10, 19, 24
56 (mostly 24)	.....	184	to Nov. 1	135	August 12, October 26
56	.....	116	1930: to Feb. 24	127	December 7
56	.....	65	to Apr. 30	127	0
56 (occas. 56)	.....	31	to June 1	123	May 28, 31
36	.....	60	to July 31	123	July 8, 9, 27
36	.....	31	to Aug. 31	138	August 4, 26
56	.....	217	1931: to Apr. 5	...	None for 6 months
					September 3, 12
		730 days			October 9, 18, 27
					November 4, 11, 14, 21, 25, 29
					December 9, 13, 19, 23, 29
					January 24, 31
					February 28

output of sodium chloride was about 5 Gm., and just about covered the intake. The specific gravity of the urine showed no fixation or limitation in range. The renal function, therefore, was good. The weight reached an early equilibrium of about 135 pounds (61.2 Kg.), and never returned to the excessively high figures (175½) noted in April, 1929. There were times when the patient showed some anasarca, but it never reached the extent that it did on his last admission; this yielded to increased doses of urea, to mersalyl or to both drugs combined. For months urea was the only medicament, and the patient continued to be edema-free and restored in cardiac efficiency.

Case 5.—J. R.,[3] a man, aged 49, came to the Montefiore Hospital on March 12, 1927. His weight was 145 pounds (65.8 Kg.). He had had recurrent attacks of congestive heart failure, and his signs were advanced and unrelieved on admission. The clinical diagnosis was generalized arteriosclerosis, hypertension and associated myocardial damage and marked congestive heart failure with no auricular fibrillation.

3. This case, as well as case 4, was reported at the New York Bronx County Medical Society by Dr. L. Tarr in June, 1929, as showing a good response to the continued use of urea up to that time.

The heart failure was progressive, large quantities of edema fluid collecting in the abdomen and thorax. The first six months he took digitalis almost daily, and the initial twenty-nine days of this period no urea was given. The next one hundred and eight days urea was added, in doses of from 48 to 24 Gm. daily, but, thereafter, for one hundred and forty-two days, he again took no urea. During the two hundred and seventy-nine days, he required several abdominal and thoracic paracenteses, and these procedures, together with several injections of mersalyl, brought the weight down to 157 pounds (72.1 Kg.), which had previously mounted to 181½ pounds (82.3 Kg.). Many and various other diuretics were also tried during this period, but with little success; the cardiac function remained poor, and the anasarca, as indicated by the huge weight, was unrelieved except by the mechanical withdrawal of collected fluid. For one hundred and fifty-two days urea was then withheld, and his condition showed very little improvement. When urea

TABLE 5.—*Treatment and Results in Case 5*

Daily Grams of Urea	Admission Weight, Pounds	Days on Urea		Weight, Pounds	Mersalyl (2 Cc.)	Digitalis
0	145	29	1927: Mar. 12 to Apr. 12	...	.....	1 cc. daily
48 to 24	...	108	to July 29	167 (181½)	Aug. 8 Oct. 21, 24, 28 Nov. 2, 6, 12, 16	1 cc. daily 1 cc. daily 1 cc. daily
0	...	142	to Dec. 18	157	Dec. 28	Sept. 12, stopped
56 or more	...	227	1928: to Aug. 2	152, 164, 169	Feb. 17	
0	...	152	1929: to June 1	...	Nov. 3, Dec. 25	
56	...	322	to Nov. 20	148	Jan. 1, Feb. 18 Mar. 29, Aug. 16, Sept. 3	
56 or more	...	410	Nov. 24, 1929 to Jan. 7, 1931	147–150	1929: Dec. 13, 20, 29 1930: Jan. 21, 30 Mar. 6, 26 Dec. 9, 16	
Jan. 10, 1931: ceased		1,067 days on urea 1,390 days in hospital				

was resumed, 56 Gm. daily, over the next three hundred and twenty-two days with very infrequent injections of mersalyl, the weight was reduced to 148 pounds, and he became unmistakably improved. Practically the same dose of urea was administered daily during the remainder of his life, four hundred and ten days, and he remained stabilized in weight, from 148 to 150 pounds (67.1 to 68 Kg.), requiring mersalyl at very rare intervals, if at all. Digitalis was not employed after the early six months' trial.

The patient's improvement, especially in the latter half of the course, was marked while he was taking urea, supplemented by mersalyl. Over many consecutive months urea alone was employed, and during the latter half of his stay in the hospital, while on urea therapy, he required no further paracenteses. He was in the habit of drinking large amounts of water, but he eliminated large quantities of urine (about 3,200 cc. daily). His chloride output was 2.06 Gm. daily over a period of many days, an amount slightly less than his intake. There were times when he gained in weight gradually, although he was taking urea, but during this period of slow gain in weight he did not require mersalyl frequently. When urea was discontinued for a short time, his weight increased at a far greater rate and his condition called for mersalyl more frequently. The renal function showed

some alteration; i. e., the range of the specific gravity became contracted (from 1.010 to 1.015); on several occasions, the blood urea nitrogen, the drug having been stopped in a test period, remained high. At autopsy the clinical diagnosis was confirmed, and arteriosclerotic changes were found in the kidneys to explain the disturbance in renal function.

THE DIURETIC VALUE OF UREA WHEN GIVEN OVER LONG PERIODS IN LARGE QUANTITIES

The use of urea as a diuretic is not new. As early as 1892, Friedrich [4] had empolyed it in comparatively small doses (from 2 to 14 Gm. daily) in cases of cardiac edema and in cases of ascites associated with cirrhosis of the liver. Klemperer [5] in 1896 also successfully employed it in cases of hepatic ascites, using slightly larger doses (from 10 to 20 Gm.). Strauss [6] in 1896 and again in 1921 emphasized the importance of urea as a diuretic. Feilchenfeld [7] in 1918 obtained excellent results, giving as much as 100 Gm. daily in cases of edema with normal renal function. Volhard [8] in 1918 used large doses of from 40 to 60 Gm. of urea per day in the treatment of patients with renal diseases; he obtained excellent results in cases of nephrosis. In 1921, McLean [9] included urea in large daily doses in his list of useful diuretics for renal edema, especially for that of nephrotic origin. Crawford and McIntosh [10] in 1923 gave the drug, in amounts up to 60 Gm. daily, to eight edematous patients, and seven of them became completely edema-free. King [11] in 1927 reported on the use of urea and diets high in protein for patients with edema; his results varied in relation to the rate of elimination of urea and renal impairment. Goldring [12] in 1929 attempted to use urea for four patients with edema, but in all of them gastric disturbances developed and the administration of the drug had to be stopped. Volhard,[13] in a discussion on the treatment for edema,

4. Friedrich, W.: Eine Abhandlung über die diuretische Wirkung des Harnstoffs, Magyar orvosi arch. **1**:400, 1892.

5. Klemperer, G.: Berl. klin. Wchnschr. **33**:6, 1896. Klemperer, G., and Dunner, L.: Behandlung der Nierenkrankheiten, Therap. d. Gegenw. **60**:57, 1919.

6. Strauss, H.: Charité-Ann. **21**:288, 1896.

7. Feilchenfeld, J.: Ueber Harnstoff als Diureticum, Therap. d. Gegenw. **59**:273, 1918.

8. Volhard, Franz: Die doppelseitigen hämatogenen Nierenkrankheiten, Berlin, Julius Springer, 1918.

9. McLean, H.: Modern Methods in the Diagnosis and Treatment of Renal Disease, Philadelphia, Lea & Febiger, 1921.

10. Crawford, J. H., and McIntosh, J. F.: The Use of Urea as a Diuretic in Advanced Heart Failure, Arch. Int. Med. **36**:530 (Oct.) 1925.

11. King, S. E.: M. Clin. North America **10**:963 (Jan.) 1927.

12. Goldring, W.: Edema in Congestive Heart Failure, Arch. Int. Med. **44**:465 (Oct.) 1929.

13. Volhard, Franz, in von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, ed. 2, Berlin, Julius Springer, 1931, vol. 6, pt. 1, p. 356.

stated that he had given urea in large doses for many weeks. He quoted a case of Strauss', in which the patient took 12 Kg. of urea during six months. It is therefore apparent that in the hands of a number of workers good and even excellent diuresis was secured when urea was given in adequate amounts. The workers all seem in agreement that urea is absorbed quickly, promptly raising its concentration in the blood, and is rapidly excreted, transporting with it large amounts of fluids to the kidneys, and that all this takes place without provoking, at least in nonrenal cases, any toxic or harmful effect. There are, however, few, if any, similar observations on the very prolonged administration of urea in massive doses.

Our study, therefore, was undertaken to ascertain whether the well functioning kidney, as in our patients with cardiovascular disease, retained its ability to rid the body of large quantities of fluid in the face of continued and repeated daily demands on it when urea is administered in large amounts over many months or years. The duration of its use in some of our cases extended over several years, a period considerably longer than that hitherto reported in the literature.

Diuretic Effect of Urea.—Unlike the distribution of sodium chloride in the body with its predilection for storing chiefly in the skin whence it is called on as needed, urea reaches the blood and all organs in practically equal concentration (Schoendorff [14] and Marshall and Davis [15]). As there is no special depot for urea, it is apt after large doses to accumulate in the blood stream in high concentration, disappearing as the drug is stopped. This high concentration of blood is a material factor in urea diuresis.

While we have reported the cases of five patients who showed beneficial results over long periods of time, there are a number who failed to show this response. The factors limiting the effectiveness of urea diuresis are being investigated at present.[16] In some patients in whom the diuretic response at the beginning of urea therapy was negligible, we witnessed good diuresis at a later date under seemingly identical conditions (case 5). Furthermore, the dose for optimum and maximum diuresis was not constant. Generally, the best and most prolonged diuresis followed from the daily ingestion of 56 Gm. divided into three equal portions. When small doses were given, edema reappeared slowly and steadily, and the dose had to be raised to 36 or even 56 Gm. daily.

Various other diuretics were also employed, either in combination with or as an alternative to urea. These we may classify, for practical

14. Schoendorff, cited by Loeb, E.: Edema, Med. Monog. **8**:77, 1923.

15. Marshall and Davis: J. Biol. Chem. **18**:53, 1914. Weiss and Vaughan: J. Lab. & Clin. Med. **7**:229, 1921.

16. Future publication by Dr. L. Tarr.

purposes, into several groups; their action is not identical and often unknown, and they possess individual differences and indications for use. In the first group we place urea. The second consists of acid and base-forming drugs: ammonium chloride, ammonium nitrate, monobasic sodium phosphate, alkalis, like soda bicarbonate in large amounts, or potassium citrate. The third group comprises metal preparations: merbaphen and mersalyl, mercurial products and bismuth salts. In the fourth we may group the purine drugs, caffeine, theobromine, theocine and also the newer preparations containing calcium, salicylates, etc. Digitalis makes up the fifth group.[17]

Restrictions in fluids (Karell regimen) or in sodium chloride (salt-poor or salt-free diet) were frequently resorted to, but for periods of many months in succession urea was the only measure used for combating edema, and no restrictions were made with regard to the quantity of water and salt within ordinary dietary limits. Throughout other stretches of many months urea was the sheet anchor of diuretic therapy, but from time to time required supplementation with mersalyl or other diuretics, or more stringent supervision of the intake of water and salt. Without entering into too many details, it may be said that our general plan consisted in ridding the patient of edema and restoring cardiac function as soon and as efficiently as possible, and we learned that this could often be accomplished expeditiously by massive doses of urea often with interval doses of mersalyl. Digitalis was not necessary. The response was equally good in the congestive failure state, whether or not the patient was suffering from auricular fibrillation. The patients who reached the hospital in previous years, i. e., before we began to give urea in massive doses, went through preliminary treatment with all the remedial agents then known, but for them, also, we finally learned to lean chiefly on urea for daily treatment. Whatever the antecedent treatment, urea became the mainstay in the cases here reported; the patients remained edema-free, usually ambulatory, restored in cardiac competency to a noticeable degree and able to take fluids and sodium chloride without hampering regulations.

We have reached the following conclusions in regard to the prolonged administration of urea in massive doses in the treatment for cardiac dropsy: 1. A marked drop in body weight results from the loss of fluids. That this loss is not flesh may be deduced from the fact that the patients in the cases reported received a diet of adequate calories (about 2,000 per day), and that they did not grow asthenic or emaciated and so-called cardiac cachexia did not develop. 2. The loss in

17. The hormone products go to make up a sixth group; that is, pituitary extracts as used in diabetes insipidus, thyroid substances in nephrosis and parathormone in cardiovascular renal edema. These products were not given in the cases here reported.

edema was greatest and most noticeable when there was pronounced congestive heart failure; subsequently, as the edema became milder its disappearance was not so spectacular. Excluding a few cases that proved to be refractory to urea, the diuretic action of urea was seldom lost completely unless and until the cardiac reserve was at a very low ebb and restoration of cardiac competency, to any appreciable degree, was no longer possible. 3. Urea was seen to stabilize the body weight at a fairly constant level over months; once this level was attained, it never reverted to the original water-logged body weight as long as urea therapy was kept up. This residual edema-free weight became quite stationary, varying but a few pounds, if at all, over months.

In the presence of this residual, almost stationary, edema-free weight there were a number of distinguishing features: (*a*) Signs of congestive heart failure were not present. With apparently good heart function and steady unchanging weight, the question arose, was urea really acting to prevent the reaccumulation of edema, or did the edema fail to reappear because of the improved state in the cardiovascular system? While we cannot speak categorically, we believe that probably both factors played significant rôles, and we have suggestive evidence that urea was by no means secondary or negligible in usefulness (case 2 and the case of W. T.). When the cardiac reserve was very poor, however, the danger of heart failure was imminent, especially if a new complication, such as a respiratory infection, ensued, and this despite the fact that congestive signs were absent and that urea was being taken in sufficient quantities.[18] Therefore, in estimating the complete loss of edema and the congestive signs, one should exclude, by fluoroscopy, signs of partial or incomplete cardiac insufficiency that had failed to spread beyond the confines of the pulmonic and hepatic circuits. These latter changes were seen to linger long after the "external," more discernible signs disappeared, and such patients might, therefore, have been erroneously labeled edema-free and without cardiac insufficiency.

(*b*) A second distinguishing feature was the fact that mersalyl had little effect at this stage. (Our charts often showed that some eager advisor ordered mersalyl when it was not needed.)

(*c*) The patients at this stage, i. e., with a residual edema-free weight, enjoyed an improved state of cardiac reserve as far as was compatible with the underlying cardiovascular derangement.

To summarize, urea did not lose its diuretic effect over long periods of time, and it helped maintain the patient's weight at a constant

18. After the "external" signs of edema disappear, the patient may still reveal, on fluoroscopy, lung stasis, engorgement of the secondary pulmonic branches and left auricular enlargement. These fluoroscopic findings speak for the continued presence of cardiac insufficiency; further or increased doses of urea are indicated.

residual, edema-free level.[19] Moreover, this equilibrium in body weight served as an excellent guide in watching for disturbances in cardiac competency or in estimating the continued diuretic efficacy of urea.

THE INNOCUOUSNESS OF THE PROLONGED USE OF MASSIVE AMOUNTS OF UREA

In estimating the possible injurious effects from the prolonged use of urea, we have three means at hand: (1) clinical observations and impressions, (2) laboratory investigations on renal function and (3) histologic study of the kidney structures.

1. Observation of cases continuously for many months, as was done under rather unchanging external circumstances in our study, enforced

TABLE 6.—*Results of Concentration Tests of the Urine and Studies of the Blood Chemistry in the Five Cases Reported*

			Before Urea Therapy				After Urea Therapy	
Case	History No.	Auricular Fibrillation	Urinary Specific Gravity	Blood Urea Nitrogen, Mg.	Days on Urea	Days in Hospital	Urinary Specific Gravity	Blood Urea Nitrogen,* Mg.
1	58046	+	1.033-1.035	24.2	243	361	1.016-1.026	24.2
2	61686	+	1.008-1.027	17.4- 9.6	383	478	1.013-1.026	17.4-26.0
3	60139	0	1.014-1.020	18.6-13.0	606	606	1.017-1.027	18.6
4	60249	0	1.018-1.009	15.0	730	730	1.024-1.034	15.0
5	53316	0	1.012-1.024	18.2-15.1	1,067	1,390	1.012-1.015	24.2-20.2

* These figures were obtained after urea had been withheld for several days before the test was performed.

the belief that urea, as we gave it, induced no outward results except for occasional gastro-intestinal distress in the way of nausea or vomiting, or occasionally diarrhea.

2. The laboratory tests did not disclose any disturbance in renal function attributable to urea. In four patients there was no change whatsoever. In one case (case 5), there were no signs of renal impairment on admission or for many months later. Subsequently, although urea served well as a diuretic, an underlying, developing arteriolar disease, confirmed at autopsy, manifested itself by a moderate impairment of renal function; i. e., the specific gravity of the urine became 1.012 and 1.015. A more detailed survey of the values of the blood urea of this patient disclosed that, with few exceptions, the figures fell promptly when urea was stopped, and that as late as Jan. 20, 1930, the blood urea nitrogen was 20.2 mg. after a three day withdrawal of the drug.

19. Seasonal variations, and also fever from one cause or another, were not without some influence on the body weight.

Concentration tests of the urine and studies of the blood chemistry, carried out after long periods during the use of urea, demonstrated little or no difference from the values obtained soon after the patients were admitted to the hospital. These results are adequately illustrated in table 6 and call for no further comment.

3. The effect of urea was determined by histologic examination of the kidney. We were able to secure microscopic preparations of the kidney from three patients (nos. 4904, 14301 and 18357) who took massive doses of urea intermittently during many months. In none did we find a pathologic alteration that could be attributed to the urea. In fact, the histologic appearance was normal except in one other case (case 5), in which a concomitant arteriolar change had taken place. Urea, therefore, in the doses and manner employed by us is without demonstrable effect on the renal structures.

MASSIVE DOSES OF UREA AS A PROPHYLACTIC AGAINST THE REACCUMULATION OF EDEMA

With the greater part of the edema fluid out of the body, urea will still mobilize any lingering or residual edema, the latter often indicating a temporary or mild degree of cardiac insufficiency. There comes a time, however, when the heart rights itself functionally and edema is entirely absent, as nearly as one can tell, and the further use of urea is unnecessary. We could not always recognize the point at which cardiac sufficiency was entirely restored and called for no further diuretic therapy. From a practical standpoint, therefore, we believed it more prudent not to halt the administration of urea, although in some cases it probably no longer played a part in preventing the recurrence of edema.

Under such circumstances, it was natural, as already indicated, to speculate whether edema failed to reappear because the heart was no longer insufficient or because the urea acted as a preventive. Our evidence, though indirect, supports the latter point of view. We observed patients, who, while taking urea, were seemingly restored to good cardiac function over long periods, free from edema and stationary in weight,[20] but in whom, when urea was discontinued, clinical signs of insufficiency soon developed and a rise in weight occurred; these signs disappeared when urea was resumed.

Two cases illustrate this change: case 2, already described, and the case of Mrs. W. T., aged 42, a private patient of one of us (Dr.

20. A small elevation in weight, of itself, say from 3 to 5 pounds (1.4 to 2.3 Kg.), was not always an infallible mark of the return of cardiac insufficiency, because such variations were governed by a variety of extracardiac circumstances, such as an increase in body flesh, changes in external temperature and humidity or a subsidence of a concomitant fever.

Miller), who had intense heart failure with extensive anasarca three and a half years prior to the writing of this article due to an advanced, chronic, rheumatic, valvular disease associated with permanent auricular fibrillation. She remained edema-free, stabilized in weight, at from 130 to 134 pounds (59 to 60.8 Kg.), and restored almost to the activity of a normal person while taking 70 Gm. of urea three or four days a week from Feb. 28, 1928, until July 20, 1931. During these months, she also received eighty-nine injections of mersalyl, the last one on April 10, 1931, and occasional doses of digitalis to control the heart rate. As a test, on May 9, 1931, with the weight at 131 pounds (59.4 Kg.) and as she had felt well and fit for months, the urea was discontinued. Within nine days, unmistakable dyspnea, increased cyanosis, edema of the ankles and tenderness of the liver developed and her weight increased 8 pounds (3.6 Kg.) (139 pounds [63 Kg.]). She became and felt sick, but was quickly restored with diuretics, taking no digitalis.

Such occurrences permit us to believe that urea is valuable in preventing the return of edema, and in this way provides another safeguard for cardiac patients with a restricted reserve in whom edema might otherwise reappear on a slight provocation.

CONCLUSIONS

1. Urea administered in the way described has been found to be an effective diuretic over long periods of time in selected cases. Whereas it can function alone over many months in keeping the patient edema-free, it may require the supplemental use of other diuretics. This is true for the patient with or without auricular fibrillation. Cases are reported in which its unbroken administration continued over three years.

2. Urea does not impair the function of the kidneys or alter their histologic structure after prolonged administration.

3. Once the signs of congestive heart failure have been removed, urea is valuable in preventing their recurrence. The drug tends to maintain the patient's weight at a low and constant edema-free level over months and even years. During such periods, our patients often required little or no restrictions of the intake of fluid or salt within ordinary dietary limits.

TRYPTOPHANURIA AND ITS SIGNIFICANCE

A PRELIMINARY REPORT

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It came to my attention about two years ago, as previously reported in the ARCHIVES,[1] that the Boltz test for tryptophan may be applied directly to urine, and, as very few data on the incidence of tryptophan in urine are available, it seemed to me that this problem was one worthy of the expenditure of some time and energy. This paper is consequently a report of the results of 169 tests on 10 normal controls, indicating that tryptophan is not eliminated in the urine of the normal man in health and on an average diet; of 525 tests on specimens sent to the laboratory for routine examination from general surgical and medical cases, and of over 600 tests on specimens from cases of nervous and mental diseases—all accumulated during the past eighteen months.

An essential improvement in the technic of the original Boltz test when employed in urinalysis has been found to consist in cooling the tube containing the test solutions during the addition of the sulphuric acid. This keeps down to a minimum the production of interfering yellow and brown colors, and renders the test much simpler to read with certainty, as evidenced by the fact that it has been easily learned by other technicians. As now employed the test is conducted as follows.

EXPERIMENTAL DATA

Technic.—Place in a small glass test tube 1 cc. of the filtered or centrifugated specimen to be examined.

Add 0.3 cc. of acetic anhydride and shake.

While the tube is held under the tap or in a large beaker of cold water, add 0.8 cc. of concentrated sulphuric acid from a pipet, a drop at a time, and shake.

Let the tube stand at room temperature under observation for five minutes.

The positive reaction is indicated by the appearance of color varying from light lilac to deep purple. The color is unmistakable by daylight, as normal specimens range from light to dark brown, but the test is practically impossible to read by any of the artificial lights with which I have experimented up to the time of writing.

Experimental Observations.—During the course of the application of the test to date, the following observations having a technical bearing have been made: Positive specimens left standing at room temperature over night without a preservative have shown in the morning considerable growth of bacteria and have been found negative by the test. The

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1. Brice, A. T.: The Boltz Test in Urinalysis, Arch. Int. Med. **46**:778 (Nov.) 1930.

same specimens preserved with a few drops of chloroform, ether or toluene remained positive. By the addition of a few drops of toluene, specimens kept at room temperature in stoppered flasks have been preserved for as long as a month. Mercuric chloride solutions precipitate tryptophan from urine and preserve it against bacterial decomposition.

Twenty specimens from general surgical and medical cases giving positive Boltz reactions in the presence of acetone and diacetic acid have been observed and recorded. Seven specimens from five different cases of diabetes mellitus have been observed and recorded positive for tryptophan by the Boltz test in the presence of sugar. The presence of acetone, diacetic acid and sugar, even in considerable amounts, therefore, does not necessarily mask a positive Boltz test. The removal of ammonia by permutit, of phosphates and carbonates by barium chloride and hydroxide or of carbohydrates by copper sulphate and calcium hydroxide from the average specimen of urine does not appreciably simplify the reading of the Boltz reaction or increase its sensitiveness through any clarification of interfering colors. The exact sensitiveness of the test up to the present time has not been determined. It is believed to be amply sensitive to demonstrate a clearcut and easily readable reaction with pathologic positives.

Pathologic Observations.—Tryptophan was found to be present in 33 per cent of 525 specimens examined from general surgical and medical cases. Of 313 of these specimens that were positive for albumin, 91, or 29 per cent, were also positive for tryptophan. The highest incidence of tryptophan in combination with albumin of any group of specimens from similar cases was shown by the group of 25 specimens from 9 different cases of degenerative diseases of the kidneys, 18 of which, or 72 per cent, were also positive for tryptophan. The finding of 222 specimens positive for albumin by the usual routine tests which were negative for tryptophan by the Boltz test indicates the existence of albuminurias in which the protein molecule eliminated does not contain a tryptophan group. A total of 169 specimens in this series was found positive for tryptophan by the Boltz test, of which number 78 or 46 per cent of the positives were albumin-free. This indicated the existence of a tryptophanuria as a clinical entity distinct from albuminuria.

The highest incidence of free tryptophan not in combination with albumin was found in a small group of 5 cases of nervous disorders, such as neuritis, neurasthenia, hysteria, neuroretinitis, and such as occur during menopause, and in 7 cases of surgical shock, such as amputation, gunshot and other wounds, fracture, dislocation and secondary hemorrhage. The figures, while meager, led me none the less to the conclusion that tryptophanuria as a distinct clinical entity might most likely be found in the group of nervous and mental disorders. This conclusion has been partially

verified by the examination during the past three months of over 600 specimens from 101 cases of mental disease, as follows: miscellaneous diagnoses, 7; dementia paralytica, 7; manic-depressive psychosis, 7, and dementia praecox, 80. The average incidence of specimens positive for tryptophan was slightly less than that for those from general surgical and medical cases, being but 21 per cent, this finding, however, representing almost entirely free tryptophan not in combination with albumin. Of the 101 cases examined by the test, 8 in the dementia praecox group have been found in which tryptophanuria was consistently present with no concurrent albuminuria.

The evidence is rather strongly indicative that tryptophanuria in nervous and mental disease is most likely to occur during periods of hyperactivity. This conclusion was arrived at by a consideration of the findings in individual cases and is supported by the following figures: Of 350 specimens taken at random from the 4 halls of a ward of the United States Veterans Hospital at Palo Alto, 50 specimens, or slightly over 14 per cent, were found positive, while of 258 specimens taken in the tub room of the same ward, 79, or about 31 per cent, were positive.

The findings with reference to the effect of tubs and packs indicate that this treatment is more likely to increase tryptophanuria than to diminish it, and that the extent of the increase is proportional to the length of time of such treatments as follows: Of 113 specimens examined just prior to the treatment, 27 per cent were found positive. Of 91 specimens examined after from two to four hours of the treatment, 31 per cent were found positive. Of 29 specimens examined after from five to seven hours of the treatment, 34 per cent were found positive. Of 25 specimens examined after over seven hours of the treatment, 40 per cent were found positive.

The patients and staff of the United States Veterans Hospital No. 24, and in particular those of ward No. 17, gave valuable cooperation and assistance in carrying out this series of tests.

SUMMARY AND CONCLUSIONS

1. An improved technic for the application of the Boltz test to the detection of tryptophan in urine is presented.

2. The application of the test is not interfered with by the presence of sugar, albumin or acetone and diacetic acid in the specimen.

3. The findings to date indicate the existence of albuminurias in which no tryptophan group is associated with the protein molecule eliminated, and also of an uncomplicated tryptophanuria.

4. Tryptophanuria as evidenced by a positive Boltz reaction undoubtedly signifies some underlying derangement of protein metabolism, though its exact pathognomonic significance, if any, is as yet not clearly understood.

CALCIUM STUDIES

VII. THE CALCIUM AND INORGANIC PHOSPHORUS CONTENT OF CEREBROSPINAL FLUID AND BLOOD SERUM IN CHRONIC GLOMERULONEPHRITIS WITH UREMIA

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PHILADELPHIA

Since Greenwald,[1] in 1915, reported the observation of an increase in the concentration of inorganic phosphorus in the blood serum of patients with nephritis, many investigators have studied the inorganic constituents of the blood and other body fluids in renal disease. Marriott and Howland [2] appear to have been the first to report the occurrence of hypocalcemia in renal failure, a phenomenon they attributed to the increase in the concentration of serum phosphate. They also suggested that the latter factor is of importance in the production of nephritic acidosis. The intimate relationship between hyperphosphatemia and hypocalcemia was soon after demonstrated by Binger,[3] who showed that the intravenous injection of phosphates is followed by a diminution in the concentration of serum calcium. Subsequent studies have confirmed these observations and have in part supported the conception of the etiologic relation of hyperphosphatemia to hypocalcemia in nephritis. Halverson, Mohler and Bergeim [4] found serum calcium values as low as 7 mg. per hundred cubic centimeters in some cases of nephritis. Feigl,[5] in a series of patients with renal disease, found the serum inorganic phosphorus to vary from 7.2 to 14.5 mg. and the serum calcium from 7.4 to 10.3 mg. per hundred cubic centimeters. Denis and Hobson [6] observed phosphorus values as high as 10 mg. and calcium values as

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From the Laboratory of Biochemistry, Jefferson Hospital, and the Department of Medicine, Jefferson Medical College.

1. Greenwald, I.: The Estimation of Lipoid and Acid-Soluble Phosphorus in Small Amounts of Serum, J. Biol. Chem. **21**:29, 1915.

2. Marriott, W. McK., and Howland, J.: Phosphate Retention as a Factor in the Production of Acidosis in Nephritis, Arch. Int. Med. **18**:708 (Nov.) 1916.

3. Binger, C.: Toxicity of Phosphates in Relation to Blood Calcium and Tetany, J. Pharmacol. & Exper. Therap. **10**:105, 1917-1918.

4. Halverson, J. O.; Mohler, H. K., and Bergeim, O.: The Calcium Content of the Serum in Certain Pathological Conditions, J. Biol. Chem. **32**:171, 1917.

5. Feigl, J.: Neue Beiträge zur Kenntnis der anorganischen Stoffe des Blutes: I. Kationen und Hyperphosphatämie bei Morbus brightii, Ztschr. f. physiol. Chem. **3**:280, 1920.

6. Denis, W., and Hobson, S.: A Study of the Inorganic Constituents of the Blood Serum in Nephritis, J. Biol. Chem. **55**:183, 1923.

low as 7.6 mg. In an earlier report Denis and Minot [7] noted serum phosphorus concentrations as high as 40 mg. per hundred cubic centimeters.

The clinical significance of these observations has been the subject of considerable discussion and speculation. Most observers believe that hyperphosphatemia in nephritis is a direct result of renal functional insufficiency and, as pointed out by Marriott and Howland,[2] is an important factor in the production of acidosis. However, Denis and Minot [7] found that the degree of phosphatemia bore no definite relation to the state of the alkaline reserve or to the degree of nonprotein nitrogen retention in the blood. In spite of this they made the observation that the serum phosphate level is of definite prognostic significance as in the nonfatal cases in their series, although the patients were seriously ill, they exhibited little or no phosphate retention. Schmitz, Rhodenburg and Myers [8] stated that a low plasma carbon dioxide combining power may be present in association with a normal serum phosphate concentration in nephritis, but that a high serum phosphate concentration is almost invariably accompanied by a low plasma carbon dioxide capacity. They also emphasized the prognostic significance of hyperphosphatemia in renal disease, but believed it to be of less value than creatinine retention. De Wesselow [9] found that the concentrations of urea and inorganic phosphorus in the blood paralleled each other, and he believed that uremic symptoms are related more directly to the latter than to the former.

In attempting to determine the significance of hypocalcemia in nephritis, one encounters a much more complex problem. Following the suggestion of Marriott and Howland [2] and the experimental work of Binger,[3] the earlier investigators attributed the diminution in serum calcium entirely to the increased serum phosphate concentration. In 1923, however, Salvesen and Linder [10] demonstrated the existence of a parallelism between the serum protein and serum calcium concentrations, showing that in cases of renal disease with diminution in the level of serum protein there is a corresponding decrease in the serum calcium concentration which is independent of any alteration in the serum phos-

7. Denis, W., and Minot, A. S.: A Study of Phosphate Retention from the Standpoint of Blood Analysis, Arch. Int. Med. **26**:99 (July) 1920.

8. Schmitz, H. W.; Rohdenburg, E. L., and Myers, V. C.: The Inorganic Phosphorus and Calcium of the Blood in Nephritis, Arch. Int. Med. **37**:233 (Feb.) 1926.

9. de Wesselow, O. L. V.: On the Phosphorus and Calcium of the Blood in Renal Disease, Quart. J. Med. **16**:341, 1923; The Immediate Prognosis in Nephritis: With Some Remarks on Uremia, Lancet **2**:163, 1923.

10. Salvesen, H. A., and Linder, G. C.: Observations on the Inorganic Bases and Phosphates in Relation to the Protein of Blood and Other Body Fluids in Bright's Disease and in Heart Failure, J. Biol. Chem. **58**:616, 1923.

phate level. Rona and Takahashi [11] several years before, and many observers since that time, had established the partition of serum calcium into diffusible and nondiffusible fractions, the latter being in all probability in combination with serum protein. This observation was borne out by the work of Salvesen and Linder.[10] Not only did they find a parallelism between changes in serum protein and calcium, but they also noted that the calcium content of practically protein-free edema fluids in renal and cardiac disease corresponded closely to the diffusible fraction of the serum calcium. However, the values (from 50 to 70 per cent) given by them as normal for this fraction are higher than those accepted at the present time. The observation was made that in two patients with uremia the decrease in calcium was out of proportion to the fall in protein and that in such cases the degree of hypocalcemia was proportional to the increase in serum phosphate. Since then Loeb and Nichols [12] and Hastings, Murray and Sendroy [13] have shown that the solubility of calcium in both true and artificial serum is increased by proteins, probably through the formation of an un-ionized, nondiffusible calcium-protein complex. It would therefore be expected that any diminution in serum protein, other things being equal, should be associated with a decrease in the concentration of serum calcium, the diminution occurring entirely in the nondiffusible fraction. Such findings have been reported in nephritis and nephrosis by Liu,[14] Scriver,[15] Cantarow,[16] Peters and Eiserson [17] and Bennett, Dodds and Robertson.[18]

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11. Rona, P., and Takahashi, D.: Beitrag zur Frage nach den Verhalten des Calciums in Serum, Biochem. Ztschr. **49**:370, 1913.

12. Loeb, R. F.: On the Diffusibility of the Calcium of Blood Serum Through Collodion Membranes: The Effect of Sodium Chloride and Changes in Hydrogen-Ion Concentration, J. Gen. Physiol. **6**:453, 1924; The Effect of Pure Protein Solutions and of Blood Serum on the Diffusibilty of Calcium, ibid. **8**:451, 1926. Loeb, R. F., and Nichols, E. G.: Factors Influencing Diffusibility of Calcium in Human Blood Serum, J. Biol. Chem. **72**:687, 1927; Effects of Dialysis and of Ether Extraction on Diffusibility of Calcium in Human Blood Serum, ibid. **74**:645, 1927.

13. Hastings, A. B.; Murray, C. D., and Sendroy, J., Jr.: Studies of Solubility of Calcium Carbonate in Salt Solutions and Biological Fluids, J. Biol. Chem. **71**:723, 1926-1927.

14. Liu, S. H.: The Partition of Serum Calcium into Diffusible and Nondiffusible Portions, Proc. Soc. Exper. Biol. & Med. **24**:817, 1927; Chinese J. Physiol. **1**:331, 1927.

15. Scriver, W. deM.: Observations on the Excretion of Calcium in Two Cases of Nephrosis Treated with Parathyroid Extract, J. Clin. Investigation **6**: 115, 1928.

16. Cantarow, A.: Calcium Metabolism and Calcium Therapy, Philadelphia, Lea & Febiger, 1931, p. 97.

17. Peters, J. P., and Eiserson, L.: The Influence of Protein and Inorganic Phosphorus on Serum Calcium, J. Biol. Chem. **84**:155, 1929.

18. Bennett, T. I.; Dodds, E. C., and Robertson, J. D.: The Conception of "Nephrosis": Observations on Three Fatal Cases, Quart. J. Med. **24**:239, 1931.

Several authors have attempted to show some relationship between the serum calcium level and uremic manifestations. Bennett [19] reported a case with serum calcium values ranging between 5.9 and 6.6 mg. and inorganic phosphorus from 6.2 to 8.5 mg. per hundred cubic centimeters, the carbon dioxide combining power of the blood plasma varying from 56 to 12.6 per cent by volume. The low calcium concentration persisted throughout the variations in the degree of acidosis, and the author expressed his belief in the possible existence of a relationship between the neuromuscular phenomena of uremia and those of tetany. Similarly, de Wesselow [9] stated that the hypocalcemia of nephritis with uremia, associated with phosphate retention, may be the underlying cause of the generalized tremors and localized twitchings commonly observed in such patients. Schmitz, Rohdenburg and Myers [8] found that nine of thirteen patients with renal disease with serum calcium values below 7 mg. exhibited convulsions or muscular twitchings, and they concluded that a relatively high proportion of cases of terminal glomerulonephritis presenting these manifestations are found to have subnormal serum calcium concentrations.

It is unfortunate that until comparatively recently no attempt was made to identify accurately the true nature of the renal lesion and metabolic disturbance in patients with renal disease associated with hypocalcemia. In nephrosis and in nephritis with a superimposed nephrotic lesion, hypocalcemia, when present, is due largely to the diminution in serum protein which commonly occurs in association with degenerative kidney lesions. In advanced chronic glomerulonephritis with renal failure, on the other hand, hypocalcemia, when present, is primarily a result of an increase in the concentration of serum phosphate. The relationship between the concentrations of protein, calcium and phosphorus in serum has been defined by Peters and Eiserson [17] by the equation: $Ca = 7 + 0.556$ protein $- 0.255$ P, which is applicable in conditions not associated with any primary disturbance of calcium phosphate metabolism. Advances in knowledge of the factors involved in the maintenance of the normal calcium and phosphorus concentrations in the blood have greatly clarified the understanding of the changes in those elements which occur in renal disease. Very few data are available, however, as regards the distribution of calcium and phosphorus between the blood and cerebrospinal fluid in various types of renal disease. Such data should afford some insight into the distribution of calcium and phosphorus in the tissue fluids and, consequently, might shed some light on the significance of hypocalcemia in nephritis and on its relation to the development of certain clinical manifestations of uremia.

19. Bennett, T. I.: Some Problems of Nephritis, Lancet **1**:535, 1928.

The present study consists of an analysis of fourteen cases of advanced glomerulonephritis with uremia. The reported data consist of the following determinations: blood creatinine, total serum protein, serum albumin and globulin, serum calcium, serum phosphate, plasma carbon dioxide combining power and cerebrospinal fluid calcium and phosphate. The protein content of the cerebrospinal fluid was not determined quantitatively, but in no case was an increase evidenced by the Noguchi qualitative method. All blood and cerebrospinal fluid

Relationship Between Concentrations of Calcium and Phosphorus in Blood Serum and Cerebrospinal Fluid in Fourteen Patients with Advanced Nephritis With and Without Hypoproteinemia

	Blood							Spinal Fluid			
Cases	Serum Creatinine, Mg. per 100 Cc.	Serum Protein, Gm. per 100 Cc.	Serum Albumin, Gm. per 100 Cc.	Serum Globulin, Gm. per 100 Cc.	Carbon Dioxide Capacity, per Cent by Volume	Serum Phosphorus, Mg. per 100 Cc.	Serum Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.	Ratio Spinal Fluid: Serum Calcium, per Cent	Ratio Spinal Fluid: Serum Phosphorus, per Cent
1. T. C.	23.4	7.24	4.62	2.62	20	18.7	7.02	7.2	3.47	49.4	38.5
2. S. G.	11.5	6.45	4.13	2.32	22	10.3	8.51	4.0	4.08	47.9	38.8
3. H. L.	15.0	6.82	3.94	2.88	31	8.6	8.42	3.3	4.32	51.3	38.3
4. J. R.	10.5	6.21	3.81	2.40	28	8.8	8.56	3.4	3.83	44.7	38.6
5. J. T.	17.4	7.02	4.12	2.90	19	12.1	8.10	4.7	3.65	45.0	38.8
6. M. V.	18.0	6.35	3.31	3.04	24	9.4	9.02	3.5	4.12	45.6	37.2
7. R. F.	13.7	6.78	3.62	3.16	16	14.2	7.93	5.7	3.26	41.1	40.1
8. S. A.	10.2	7.16	4.08	3.08	20	10.8	8.54	4.2	3.75	43.9	38.8
Average							8.26	4.5	3.81	46.1	38.6
9. T. M.	15.8	4.22	2.06	2.16	26	7.3	7.40	3.1	4.13	55.8	42.4
10. A. F.	9.6	3.18	1.45	1.73	23	9.8	7.13	3.5	3.82	53.5	35.7
11. T. S.	11.0	3.66	1.60	2.06	18	11.6	7.22	4.5	4.04	55.9	39.6
12. L. M.	12.5	4.34	2.15	2.19	19	8.4	7.61	3.4	3.96	52.0	40.4
13. W. G.	11.5	3.05	1.38	1.67	21	8.4	6.84	3.1	4.31	63.0	36.9
14. J. W.	3.4	3.67	1.64	2.03	47	3.5	8.25	1.1	5.05	61.0	31.1
Average							7.41	3.1	4.21	56.8	37.6
Total average	5.44	....	....	..		10.1	7.89	3.9	3.98	50.7	38.2

studies in each case were made on specimens withdrawn simultaneously. Total serum proteins were determined by a micro-Kjeldahl method employing direct nesslerization,[20] serum albumin by the method of Howe [21] and serum globulin by subtracting albumin from serum protein. Calcium determinations were made by the Clark-Collip modification of

20. Hawk, P. B., and Bergeim, O.: Practical Physiological Chemistry, ed. 10, Philadelphia, P. Blakiston's Son & Company, 1931, p. 449.

21. Howe, P. E.: The Determination of Proteins in Blood: A Micro Method, J.Biol.Chem. **49**:109, 1921.

the Kramer-Tisdall procedure,[22] and inorganic phosphorus by the method of Fiske and Subbarow.[23] Creatinine was determined by the method of Folin,[24] and the plasma carbon dioxide capacity by the manometric method of Van Slyke.[25]

All of the patients in this series exhibited high grades of nitrogen retention, the blood creatinine values ranging from 3.4 to 23.4 mg. per hundred cubic centimeters, all but one (case 14, J.W.) being above 9.6 mg. All presented features characteristic of chronic glomerulonephritis, six (cases 9 to 14) showing evidence of superimposed nephrotic lesions. Muscular hyperirritability was present in cases 1, 5, 7, 8, 10 and 12, manifested by generalized tremors, localized muscular twitchings or generalized or localized convulsions.

SERUM PROTEINS

The total serum protein concentration ranged from 3.05 to 7.24 Gm. per hundred cubic centimeters, serum albumin from 1.38 to 4.62 Gm. and serum globulin from 1.67 to 3.16 Gm. Edema of varying degree was present in cases 9 to 14, the total serum protein content in this group ranging from 3.05 to 4.34 Gm., the serum albumin from 1.38 to 2.15 Gm. and the serum globulin from 1.67 to 2.19 Gm. These findings are in accord with the observations of most recent investigators, which indicate that edema is usually present with serum albumin values below 2 Gm. per hundred cubic centimeters if the total protein concentration is below 5 Gm. (Leiter [26]). The serum protein content bore no discernible relation to the degree of renal insufficiency.

SERUM AND CEREBROSPINAL FLUID PHOSPHATE

The inorganic phosphorus concentration of the serum varied from 3.5 to 18.7 mg. per hundred cubic centimeters, being above 7 mg. in all but one case (case 14). The degree of hyperphosphatemia roughly paralleled the degree of creatinine retention and of acidosis as indicated by the diminution in the carbon dioxide combining power of the blood plasma. The latter relationship, however, was not invariable, for cases

22. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

23. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

24. Folin, O.: Laboratory Manual of Biologic Chemistry, ed. 4, New York, D. Appleton & Company, 1927, pp. 165 and 243.

25. Van Slyke, D. D.: Portable Form of Manometric Gas Apparatus and Certain Points in Technique of its Use, J. Biol. Chem. **73**:121, 1927.

26. Leiter, L.: Nephrosis, Medicine **10**:182, 1931

3, 4, 12 and 13, with serum phosphate concentrations of 8.6, 8.8, 8.4 and 8.4 mg., respectively, had carbon dioxide capacity values ranging from 16 to 31 per cent by volume. Furthermore, in case 12, with a carbon dioxide capacity of 19 per cent by volume, the serum phosphate was 8.4 mg. per hundred cubic centimeters, whereas in case 1, with a serum phosphate concentration of 18.7 mg., the highest observed in this series, the plasma carbon dioxide capacity was 29 per cent by volume. Obviously, factors other than phosphate retention are of importance in the production of a diminished alkali reserve in nephritis. Chief among these appear to be: (*a*) impairment of the ammonia-forming function of the kidneys, as demonstrated by Palmer and Henderson [27] and by Van Slyke and his co-workers,[28] and (*b*) depletion of the available base supply of the body by excessive elimination of base in the urine, as shown by Linder [29] and Salvesen.[30]

The inorganic phosphorus of the cerebrospinal fluid varied from 1.1 to 7.2 mg. per hundred cubic centimeters, the ratio of cerebrospinal fluid to serum phosphorus ranging from 31.1 to 42.4 per cent (average 38.2 per cent). These figures are in agreement with those of Merritt and Bauer,[31] who found this ratio to range from 31 to 45 per cent (average 38 per cent) in a group of patients with nonsuppurative disease of the central nervous system. They are somewhat lower than those reported by Hamilton,[32] which averaged 50 per cent. If one accepts the premise that the cerebrospinal fluid is a dialysate of the blood plasma, it follows that the serum phosphorus is diffusible to the extent of about 30 to 45 per cent. These observations emphasize the difficulty of interpreting results obtained by in vitro diffusibility studies, and the fallacy of accepting results obtained by such methods as indicative of conditions of diffusibility existing in the living body. For example, Pincus, Peter-

27. Palmer, W. W., and Henderson, L. J.: A Study of Several Factors of Acid Excretion in Nephritis, Arch. Int. Med. **16**:109 (July) 1915.

28. Van Slyke, D. D.; Linder, G. C.; Hiller, A.; Leiter, L., and McIntosh, J. F.: The Excretion of Ammonia and Titrable Acid in Nephritis, J. Clin. Investigation **2**:255, 1926.

29. Linder, G. C.: The Effect of Mineral Acid on Acid-Base Regulation in Health and in Nephritis, Quart. J. Med. **20**:285, 1927.

30. Salvesen, H. A.: Variations in the Serum Electrocytes in Diseases of Renal Origin with Special Reference to the Cause of Renal Acidosis, Acta med. Scandinav. **69**:126, 1928.

31. Merritt, H. H., and Bauer, W.: The Equilibrium Between Cerebrospinal Fluid and Blood Plasma: III. The Distribution of Calcium and Phosphorus Between Cerebrospinal Fluid and Blood Serum, J. Biol. Chem. **90**: 215, 1931.

32. Hamilton, B.: A Comparison of the Concentrations of Inorganic Substances in Serum and Spinal Fluid, J. Biol. Chem. **65**:101, 1925.

son and Kramer,[33] employing ultrafiltration through artificial membranes, found that the inorganic phosphorus content of the serum and ultrafiltrate were practically identical, indicating that serum phosphate is completely diffusible. This marked discrepancy can be interpreted only as indicating the distinct difference that exists between in vivo and in vitro diffusibility. This observation, pointed out by me in previous communications [34] dealing with calcium diffusibility, has not been sufficiently emphasized in the literature.

The data reported here, as well as those of Merritt and Bauer [31] and Hamilton,[32] suggest that the in vivo diffusibility of phosphorus is influenced by the serum protein content, as is that of calcium. This hypothesis is further supported by the findings of Merritt and Bauer [31] in meningitis, in which condition an increase in the cerebrospinal fluid protein concentration was associated with an increase in the ratio of cerebrospinal fluid to serum phosphorus from the normal average of 38 per cent to an average of 49 per cent. Grollman [35] found that whereas normally all of the serum phosphate was filtrable, in conditions of hypercalcemia, as induced by the injection of parathormone, only 63 per cent was filtrable. In a case of hypoparathyroidism referred to by Albright, Bauer, Cockrill and Ellsworth,[36] as the difference between the serum calcium and cerebrospinal fluid calcium diminished, the difference between the corresponding levels of phosphorus increased, and vice versa, suggesting, as stated by the authors, that in hypoparathyroidism the inactivated (nondiffusible) calcium decreases and the inactivated (nondiffusible) phosphorus increases. No such relationship is evidenced in the present series, there being no apparent reciprocal correlation between the ratios of calcium and phosphorus in cerebrospinal fluid and blood serum. The problem in nephritis, however, is complicated by the variation in serum protein which does not play an important part in the disturbance of calcium-phosphate equilibrium in parathyroid dysfunction. The constancy of the cerebrospinal fluid-blood serum phos-

33. Pincus, J. B.; Peterson, H. A., and Kramer, B.: A Study by Means of Ultrafiltration of the Condition of Several Inorganic Constituents of Blood Serum in Disease, J. Biol. Chem. **68**:601, 1926.

34. Cantarow, A.: Calcium Studies: V. The Relationship Between the Calcium Content of Cerebrospinal Fluid and Blood Serum, Arch. Int. Med. **44**:670 (Nov.) 1929; The Diffusibility of Calcium in Bronchial Asthma and Allied Disorders and in Pulmonary Tuberculosis, Am. J. M. Sc. **179**:497, 1930.

35. Grollman, A. J.: The Condition of the Inorganic Phosphorus of the Blood with Special Reference to the Calcium Concentration, J. Biol. Chem. **72**: 565, 1927.

36. Albright, F.; Bauer, W.; Cockrill, J. R., and Ellsworth, R.: Studies on the Physiology of the Parathyroid Glands: II. The Relation of the Serum Calcium to the Serum Phosphorus at Different Levels of Parathyroid Activity, J. Clin. Investigation **9**:659, 1931.

phorus ratio in this group of patients may be only apparent, the influence of the varying serum protein concentration being masked by simultaneous variations in the calcium content of serum and cerebrospinal fluid.

SERUM AND CEREBROSPINAL FLUID CALCIUM

The serum calcium concentration in the entire group varied from 6.84 to 9.02 mg. per hundred cubic centimeters, the average being 7.89 mg. In the eight patients with normal total protein values, the serum calcium ranged from 7.02 to 9.02 mg., averaging 8.26 mg.; in the six patients with hypoproteinemia the serum calcium ranged from 6.84 to 8.25 mg., the average being 7.41 mg. These subnormal values are in agreement with those previously reported and referred to. They illustrate graphically the influence of the serum proteins and phosphate on the serum calcium concentration. In the group of eight patients with normal serum protein values (cases 1 to 8), the calcium values are slightly higher than in the other six patients owing to the fact that in the former hyperphosphatemia alone is exerting a hypocalcemic influence, whereas in the latter the existence of a superimposed state of hypoproteinemia exaggerates the effect of the increased phosphate concentration. It is interesting to note the close agreement of the observed average serum calcium concentration with the calcium value calculated from the protein and phosphorus concentrations on the basis of the formula suggested by Peters and Eiserson[17]: 3.02464 (0.556 protein) — 2.01195 (0.225 P) + 7 = 8.01 (Ca). The calculated value, 8.01 mg., is only 1.5 per cent (0.12 mg.) higher than the observed value, 7.89 mg., substantiating the fundamental integrity of the quantitative expression of the equilibrium between serum protein, phosphate and calcium as elaborated by Peters and Eiserson.[17]

The cerebrospinal fluid calcium concentration in the entire series ranged from 3.26 to 5.05 mg. per hundred cubic centimeters, averaging 3.98 mg. Eliminating from consideration case 14, in which the serum and spinal fluid phosphate concentrations were within nominal limits, the highest spinal fluid calcium value was 4.31 mg. In cases 1 to 8, with hyperphosphatemia but with normal serum protein values, the spinal fluid calcium values ranged from 3.26 to 4.32 mg., averaging 3.81 mg.; in cases 9 to 13, with both hyperphosphatemia and hypoproteinemia, the spinal fluid calcium varied from 3.82 to 4.31 mg., averaging 4.05 mg.; in case 14, with normal serum phosphate and low serum protein values, the spinal fluid calcium was 5.05 mg. The normal range, as obtained in a large series of cases previously reported,[37] is from

37. Cantarow, A.: Calcium Studies: IV. The Calcium Content of Cerebrospinal Fluid, Arch. Int. Med. **44**:667 (Nov.) 1929.

4.5 to 5.5 mg., constituting from 45 to 55 per cent of the total serum calcium concentration. It appears that in nephritis with hyperphosphatemia the cerebrospinal fluid calcium concentration is subnormal. That this decrease is dependent on an increase in serum phosphate rather than on a diminution in serum protein is evidenced by the normal level observed in case 14 and by the observation that the average spinal fluid calcium concentration in cases 9 to 13 was higher than in cases 1 to 8, despite the fact that in the former group the serum calcium and serum protein values were distinctly lower than in the latter. It seems, therefore, that the concentration of nondiffusible calcium (protein-bound) has little or no influence on the diffusibility of calcium in nephritis, the cerebrospinal fluid calcium level being independent of changes in the total serum calcium level caused by variations in the serum protein concentration. This is in accord with the generally accepted conception of the partition of serum calcium into diffusible and nondiffusible components.

The ratio of cerebrospinal fluid to serum calcium ranged from 41.1 to 51.3 per cent, averaging 46.1 per cent, in the group with normal serum protein values (cases 1 to 8), and from 52.0 to 63.0 per cent, averaging 56.8 per cent, in the patients with low serum protein values (cases 9 to 14). These figures further emphasize the dependency of the cerebrospinal fluid calcium concentration on serum phosphate variations and its independence of variations in serum protein.

On analyzing the spinal fluid calcium and phosphate values, it appears that there is a roughly reciprocal relationship between these two factors, the calcium concentration diminishing as the phosphate concentration increases. This observation is of great interest in view of the similar relationship that exists between these two elements in the blood serum. It would seem that in nephritis the cerebrospinal fluid inorganic phosphorus content is the factor that determines the concentration of calcium in that fluid in the absence of an increase in its protein content.

CEREBROSPINAL FLUID CALCIUM AND MUSCULAR IRRITABILITY IN UREMIA

The relationship between the serum calcium level and manifestations of muscular hyperirritability in uremia has attracted considerable attention,[38] as was indicated previously. Several observers have suggested that the muscular twitchings and generalized tremors that commonly occur in uremia may be dependent on a state of hypocalcemia. This relationship, however, has not been found to be constant, one reason

38. Schmitz, Rohdenburg and Myers (footnote 8). de Wesselow (footnote 9). Bennett (footnote 19).

perhaps being the almost universal failure, until recently, to distinguish hypocalcemia dependent on hypoproteinemia from that dependent on hyperphosphatemia. Very few data are available regarding the diffusibility of calcium in uremia. Pincus, Peterson and Kramer,[38] on the basis of ultrafiltration experiments, stated that the decrease in serum calcium in nephritis occurs only in the nondiffusible fraction. However, their data include one case of uremia, with convulsions, in which, with a serum phosphorus value of 15.6 mg. per hundred cubic centimeters, the serum calcium was 6.3 mg., of which only 2.8 mg. was ultrafiltrable, an observation that contradicts the foregoing statement. In view of the fact that only the diffusible fraction of serum calcium is believed to be concerned with the maintenance of normal muscular irritability, the relation of the cerebrospinal fluid calcium concentration to disturbances of this function may be of significance.

In the present series, generalized or localized convulsive seizures, generalized tremors or localized muscular twitchings occurred in cases 1, 5, 7, 8, 10 and 12, with spinal fluid calcium values of 3.47, 3.65, 3.26, 3.75, 3.82 and 3.96 mg., respectively. It is interesting to note that in none of these cases was the total serum calcium concentration below 7 mg., and that in two instances it was above 8 mg. In only one case (case 4) with a spinal fluid calcium content below 4 mg. (3.83 mg.) were these manifestations of hyperirritability absent. This apparent relationship may be purely accidental. It, however, rests on a much more logical basis than does the relationship between such manifestations and the serum calcium level.

If the muscular hyperirritability of uremia is dependent on a diminution in the concentration of calcium in the spinal fluid or tissue fluids, the mechanism of its production must differ fundamentally from that operative in parathyroid tetany. It is true that in the latter condition studies of the in vitro diffusibility of calcium reveal a diminution in the ultrafiltrable or dialyzable fraction. However, studies of the in vivo diffusibility of calcium, as evidenced by the cerebrospinal fluid calcium concentration, yield quite different results. For example, Cameron and Moorhouse[39] found that in acute tetany both serum and spinal fluid calcium tend to approach the same low level, indicating, apparently, that the decrease in diffusible calcium is relatively slight, whereas the nondiffusible calcium may entirely disappear. Similar findings have

39. Cameron, A. T., and Moorhouse, V. H. K.: The Tetany of Parathyroid Deficiency and the Calcium of the Blood and Cerebrospinal Fluid, J. Biol. Chem. **63**:687, 1925.

been reported by Merritt and Bauer [40] in human beings and by Morgulis and Perley in dogs.[41] These observations emphasize the necessity for distinguishing sharply between diffusibility through living membranes, in contradistinction to artificial membranes.

Further evidence of the fundamental difference between uremic and tetanic phenomena is furnished by the work of Binger,[3] who showed that when basic or neutral phosphates are injected intravenously in amounts sufficient to lower the serum calcium, tetany results, but not if acid phosphates are employed. Since the hyperphosphatemia of advanced renal functional insufficiency is invariably associated with acidosis and with an increase in the proportion of acid phosphate in the blood and tissue fluids, the condition is analogous to that existing in the acid phosphate injection experiment of Binger.[3] Furthermore, the muscular hyperirritability of tetany is associated with a lowered threshold of excitability by electrical stimulation, a phenomenon that has not often been observed in uremia. In this fact may reside the essential difference between the two hyperirritable states.

SUMMARY

1. Hypocalcemia in advanced nephritis is dependent on hyperphosphatemia, hypoproteinemia or both.

2. The degree of hyperphosphatemia roughly parallels the degree of creatinine retention and acidosis, the latter less consistently than the former. The ratio of cerebrospinal fluid to serum phosphate ranged from 31.1 to 42.4 per cent, averaging 38.2 per cent. These figures fall within normal limits.

3. The in vivo diffusibility of phosphorus appears to be influenced by serum protein as is that of calcium, whereas its diffusibility through artificial membranes is apparently not so influenced.

4. There is no apparent reciprocal relationship between the ratios of calcium and phosphorus in cerebrospinal fluid and blood serum as exists in parathyroid dysfunction. The problem is complicated, however, by the variation in serum protein, which does not play an essential part in the disturbance of calcium-phosphate equilibrium in parathyroid dysfunction. The constancy of the cerebrospinal fluid-blood serum phosphorus ratio in nephritis may be only apparent, the influence of the varying serum protein concentration being masked by that of

40. Merritt, H. H., and Bauer, W.: The Equilibrium Between Cerebrospinal Fluid and Blood Plasma: IV. The Calcium Content of Serum, Cerebrospinal Fluid and Aqueous Humor at Different Levels of Parathyroid Activity, J. Biol. Chem. **90**:233, 1931.

41. Morgulis, S., and Perley, A. M.: Studies on Cerebrospinal Fluid and Serum Calcium, with Special Reference to Parathyroid Hormone, J. Biol. Chem. **88**:169, 1930.

simultaneous variations in the calcium content of spinal fluid and blood serum.

5. The serum calcium concentration ranged from 6.84 to 9.02 mg. per hundred cubic centimeters, being lowest in the group of patients with coincident hypoproteinemia and hyperphosphatemia. The observed serum calcium values are in close agreement with values calculated from the protein and phosphorus concentrations on the basis of the formula suggested by Peters and Eiserson.

6. The cerebrospinal fluid concentration ranged from 3.26 to 5.05 mg. per hundred cubic centimeters, averaging 3.98 mg. In thirteen cases of hyperphosphatemia the highest spinal fluid calcium value was 4.31 mg. The decrease in this factor is dependent on an increase in serum phosphate rather than on a decrease in serum protein.

7. There is a roughly reciprocal relationship between the concentrations of calcium and phosphorus in the spinal fluid, as in the blood serum, the calcium content diminishing as the phosphate content increases.

8. There appears to be some relationship between the cerebrospinal fluid calcium concentration and manifestations of muscular hyperirritability in uremia, such manifestations occurring with spinal fluid calcium values below 4 mg. per hundred cubic centimeters. The mechanism of production of these phenomena in uremia differs fundamentally from that operative in parathyroid tetany.

9. These observations emphasize the distinction that must be made between diffusibility of calcium and phosphorus through living membranes, in contradistinction to artificial membranes.

CARDIAC OUTPUT FOLLOWING ARTIFICIAL PNEUMOTHORAX IN MAN

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Measurements of the cardiac output and of certain other circulatory and respiratory functions have been made in three cases [1] of pulmonary tuberculosis both before and during the establishment of artificial pneumothorax. All three patients were young men and had moderately advanced lesions of one lung, the right in patients F.S. and A.G.; the left in patient D.R. Summaries of the histories and clinical findings are given at the end of the article.

Relatively large insufflations of air were given each time, the attempt being made to collapse the lung rapidly, in order to demonstrate as clearly as possible the effects of this procedure on the circulation. Nine hundred, 800 and 800 cc. were injected into patient D.R., with a four day interval between the first and second injections and three days between the second and third. Patient F.S. received 700, 500, 600 and 600 cc., the intervals between injections being two, two and three days. The third patient, A.G., received about 500 cc. twice a week, a total of 4,750 cc. being given in four and a half weeks.

The various measurements that were made and the data obtained are listed in the accompanying table, and the more important changes occurring during the course of the pneumothorax production in case 3 are summarized in the accompanying chart.

TECHNIC

It is to be noted that the cases were not treated just alike. The respiratory and circulatory studies on D. R. were made not under basal conditions, but with the patient at rest in bed, three or four hours after the last meal. The technic

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From the Department of Medicine of the College of Physicians and Surgeons and the Presbyterian Hospital.

1. These patients were in the tuberculosis service of Dr. James A. Miller at Bellevue Hospital, and were transferred temporarily to the Presbyterian Hospital where the studies here reported were made. The assistance and cooperation of Dr. Miller and members of his staff were received throughout the course of the work.

Patient and Date	Hour	Pneumothorax, Cc.	Intrathoracic Pressure, Cm. H_2O	Vital Capacity, Liters	Residual Air, Liters	Respirations per Min.	Pulse	Expired Air, Liters per Min.	CO_2 Output per Min., Cc.	O_2 Consumption per min., Cc.	Arterial CO_2 Content, Alveolar CO_2, Mm.	Arterial CO_2 Content, per Cent by Volume	Arterial CO_2 Tension, Mm.	Arterial p_H	Oxygenated Mixed Venous CO_2, Mm.	A-V CO_2 Difference, per Cent by Volume*	Cardiac Output, Liters per Min.†	Oxygen Capacity, per Cent by Volume	Arterial Oxygen Saturation, per Cent
D. R.‡																			
Mar. 26	11:00	.....	.....	....	....	15	90	7.08	270	314	40.4	....	....	....	48.3	3.6	7.5	19.9	..
33	3:30	.....	.....	....	....	15	86	7.28	267	301	40.8	....	....	....	50.9	4.4	6.1	....	..
Apr. 1	12:10	900	0, —4	....	....	..	....	....	....	....	....	....	....	....	....	....	....	....	..
	4:00	.....	.....	....	....	15	112	7.56	280	332	38.8	....	....	....	51.2	6.0	4.7	....	..
5	.....	800	.....	2.50	....	..	....	....	....	....	....	....	....	....	....	....	....	....	..
8	.....	800	.....	2.00	....	..	....	....	....	....	....	....	....	....	....	....	....	....	..
F. S.																			
Jan. 10	8:30	.....	.....	3.40	1.59	22	95	7.17	216	245	40.7	53.0	41.1	7.43	49.8	3.6 (3.8)	6.0 (5.7)	17.7	96
17	9:50	.....	.....	....	1.33	..	88	5.94	147	208	40.9	....	....	7.45	50.2	3.6	4.1	....	..
20	11:00	.....	.....	....	....	..	....	....	....	....	....	57.1	....	....	....	....	....	18.6	..
21	9:15	700	—1, —2	....	....	..	....	....	....	....	....	....	....	....	....	....	....	....	..
	11:00	.....	.....	1.65	0.85	26	102	6.03	180	227	43.2	47.5	41.5	7.43	53.9	3.9 (3.8)	4.6 (4.7)	18.4	88
																		17.4	99
23	8:30	.....	—5, —8	2.20	....	..	....	....	....	....	....	55.4	41.9	....	....	....	....	....	..
25, 28	.....	1,200	0, —1	....	....	..	....	....	....	....	....	....	....	....	....	....	....	....	..
28	10:40	.....	.....	....	0.65	29	102	6.15	153	201	38.1	50.2	40.0	7.42	52.5	5.7 (4.8)	2.7 (3.2)	18.4	91
31	10:30	.....	.....	2.00	0.77	26	105	7.19	169	225	37.6	47.5	36.9	7.44	49.0	4.4 (5.1)	3.8 (3.3)	18.2	87
A. G.§																			
Feb. 20	7:25	.....	.....	4.10	0.95	15	79	5.83	181	217	41.2	....	....	7.44	50.8	3.9	4.6	....	..
25	8:15	.....	.....	4.10	1.10	18	88	6.32	193	227	41.5	....	....	7.44	51.0	3.9	4.9	17.2	..
28	8:05	.....	—6, —7	4.10	1.00	17	88	6.46	194	233	42.1	53.8	41.6	7.44	51.7	3.9 (4.2)	5.0 (4.6)	17.2	94
5	8:05	500	—2, —4	2.90	0.75	24	100	6.84	187	237	42.5	....	....	7.43	52.4	4.0	4.7	....	..
6 to 13	....	1,500	—1, —2	3.65	....	..	....	....	....	....	....	....	....	....	....	....	....	....	..
14	7:57	.....	.....	....	0.85	20	96	6.17	181	233	40.2	....	....	7.45	50.8	4.4	4.1	....	..
16, 18	....	850	—1, —2	3.40	....	..	....	....	....	....	....	....	....	....	....	....	....	....	..
19	8:09	.....	.....	....	....	20	93	6.71	180	229	38.5	....	....	7.46	48.4	4.2	4.3	....	..
21	7:58	.....	.....	....	....	23	105	6.66	185	234	38.8	....	....	7.46	49.3	4.4	4.2	17.1	97
23, 26	....	900	+1, 0	....	....	..	....	....	....	....	....	....	....	....	....	....	....	....	..
30	7:50	.....	.....	....	....	22	100	6.62	186	233	36.4	49.8	37.0	7.47	47.6	4.9 (4.6)	3.8 (4.0)	17.7	96
2, 4	....	1,000	+1, —2	3.15	....	..	....	....	....	....	....	....	....	....	....	....	....	....	..
7	7:48	.....	.....	....	0.58	24	109	7.04	189	251	37.4	48.2	34.1	7.46	48.0	4.7 (6.4)	4.0 (3.0)	17.9	92

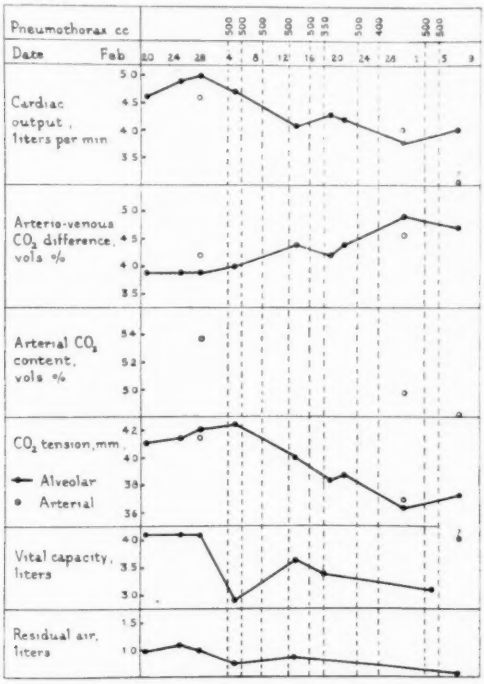
* A-V CO_2 difference is the difference between the carbon dioxide content of arterial and of mixed venous blood.

† The figures in parentheses represent cardiac output calculated by the use of arterial blood carbon dioxide content; the other figures, cardiac output calculated by the use of alveolar carbon dioxide tensions.

‡ Serum electrolyte measurements (venous blood, under basal conditions) were made on the blood of D. R. as follows: March 25, 9:10 a. m.: chloride, 102 mM.; carbon dioxide, 26.8 mM.; phosphorus, 2 mM.; protein, 17.8 mM.; total base, 149 mM.; April 2, 9:00 a. m.: chloride, 103.2 mM.; carbon dioxide, 28.1 mM.; phosphorus, 2.4 mM.; protein, 17.7 mM.; total base, 151.7 mM.

§ Venous pressures of A.G. made on March 2 were: +3.0 cm. of water; March 4, +4.5 cm.; March 9, +2.5 cm.; March 20, +4.0 cm.; April 1, +4.0 cm.

for obtaining expired air, alveolar air and mixed venous tensions has been described in previous papers.[2] Arteriovenous differences in carbon dioxide content were obtained by plotting the alveolar and (oxygenated) mixed venous tensions on a carbon dioxide dissociation curve of the patient's blood (venous blood being used in this case). The blood flow was thus determined by the Fick principle. Blood for the serum electrolyte determinations was drawn under basal conditions; these determinations were made by Miss E. M. Benedict, using the methods described by Atchley and Benedict.[3]



Changes in the circulatory and respiratory functions of A. G. (case 3) following pneumothorax. The figures at the top of the diagram indicate the amounts of air injected each time and the date when the injection was given.

In the case of patient F. S., the experiments were done under basal conditions. The blood flow determinations also differed from those on patient D. R. in several other respects: (1) the actual arterial carbon dioxide content was determined by drawing arterial blood (from the brachial artery) shortly after the respiratory

2. Richards, D. W., Jr., and Strauss, M. L.: Circulatory Adjustment in Anemia, J. Clin. Investigation **5**:161, 1928; Carbon Dioxide and Oxygen Tensions of the Mixed Venous Blood of Man at Rest, ibid. **9**:475, 1930.

3. Atchley, D. W., and Benedict, E. M.: The Distribution of Electrolytes in Dogs Following Ligation of Both Ureters, J. Biol. Chem. **73**:1, 1927.

procedure was finished (except in the experiment of January 17); (2) the arterial blood sample was also used for the construction of a point on the oxygenated whole blood carbon dioxide curve; (3) the slope of this curve was not determined experimentally, but was estimated from the oxygen capacity, a justifiable procedure,[2] especially when, as here, relative and not absolute values are important; (4) a special effort was made to have the oxygenated mixed venous tensions as accurate as possible, two samples being taken at the end of fifteen seconds', and four at the end of twenty seconds', rebreathing in each experiment; the results were good, at least three of the six values being within 0.5 mm. of each other in every blood flow determination except the first one (January 10).

Certain minor changes of technic were employed with the third patient, A. G.: 1. A Tissot spirometer was used to collect expired air instead of a Douglas bag, and the patient breathed outside air in all experiments. 2. Alveolar air samples were used in most of the experiments to give arterial blood carbon dioxide values, as the patient had at all times a sufficiently large vital capacity to insure satisfactory alveolar specimens. Arterial blood was also drawn, as a further check on the results, on three occasions; in obtaining these samples, care was taken to have the patient breathing through the mouthpiece and tubing in the same manner as when the expired air and alveolar and venous samples were taken. 3. All respiration experiments were done early in the morning under strict basal conditions. 4. A carbon dioxide dissociation curve was constructed with one sample of venous blood, and the slope of this curve was used for the determination of arterial and venous blood carbon dioxide contents. As the oxygen capacity of successive blood samples varied little, the use of this slope for all experiments seemed justified.

The residual air values also call for a word of comment. They were calculated from the increase, during rebreathing, in nitrogen percentage in the rebreathed carbon dioxide-oxygen mixture that was used for mixed venous tension determination; such an increase was, of course, due to the nitrogen in the alveolar air. The residual air values so calculated are not exact, but give an approximate estimate of the changes in residual volume that took place during the course of establishment of the pneumothorax.[2]

The course of pneumothorax production was followed in each patient by repeated fluoroscopic examinations. Dr. Kenneth B. Turner made these examinations.

Venous pressure measurements were made on patient A. G. by a technic essentially that of Moritz and von Tabora.[4] The figures given for these pressures are in terms of centimeters of water measured from the distal edge of the manubrium sterni.

RESULTS

The finding of particular interest in this study was the consistent and progressive lowering of cardiac output that took place in all three cases as the establishment of unilateral pneumothorax progressed. There was a corresponding increase in the arteriovenous carbon dioxide (and oxygen) differences. The amount of the decrease in volume flow of blood was not great, but was well outside the experimental error of the method. In general, the decrease in blood flow seemed roughly proportional, in

4. Moritz, F., and von Tabora, D.: Ueber ein Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, Deutsches Arch. f. klin. Med. **98**:475, 1910.

the three cases, to the degree of collapse of the lung, though the data were not enough to make this indication definite.

In the two cases (cases 2 and 3) in which blood studies were made, it will be noted that there was a fairly satisfactory correspondence between alveolar and arterial carbon dioxide values, except in the last arterial blood sample taken on A.G. (case 3). In this case there was almost certainly an error in the determination of the blood carbon dioxide curve; no obvious break in technic, however, was detected.

In the one case in which it was measured, the venous pressure did not change appreciably during the course of the pneumothorax. The arterial blood pressure showed no consistent variation in any of the three cases. There were no significant alterations in the total oxygen consumption or the carbon dioxide output. The pulmonary ventilation increased only slightly toward the end of the series of air insufflations. The vital capacity and residual air volumes diminished progressively. These observations are consistent with previous work.[5]

Patient D.R. showed a slight fall in alveolar carbon dioxide tension four hours after a 900 cc. pneumothorax injection; F.S. and A.G. had, during the time in which they were receiving pneumothorax treatments, a gradual and steady fall in arterial carbon dioxide content and in alveolar and arterial carbon dioxide tensions. This phenomenon was reported several years ago by Meakins and Davies.[6]

In respect to the oxygen saturation of the arterial blood, the results on F.S. differed from those on A.G. As shown in the accompanying table, the former developed a definite, though slight, arterial oxygen unsaturation, while the latter retained his normal arterial saturation percentage, except in the last experiment. Arterial oxygen unsaturation did not occur in any of Meakins and Davies' cases. We have been inclined to associate its occurrences in F.S. with the rapidity with which the lung collapse was accomplished. Clinically, both F.S. and A.G. showed mild but unmistakable cyanosis of the nail beds and lips during the latter part of their course of treatment. The explanation for this in the case of A.G., whose arterial saturation was normal, was perhaps the decrease in blood flow, with an increased tissue utilization of oxygen and a decreased venous oxygen content.

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5. Means, J. H., and Balboni, G. M.: Respiration in Pneumothorax, J. Exper. Med. **24**:671, 1916. Le Blanc, W.: Respiratorischer Gasaustausch und Lungendurchblutung, Beitr. z. Klin. d. Tuberk. **50**:21, 1922. Meakins, J. C., and Davies, H. W.: Respiratory Function in Disease, Edinburgh, Oliver & Boyd, 1925. Myers, J. A., and Bailey, W.: Vital Capacity Test in Artificial Pneumothorax Therapy, Am. Rev. Tuberc. **10**:597, 1925. Anthony and Heine: Spirographische Untersuchungen bei Lungenkollaps, Beitr. z. Klin. d. Tuberk. **71**:362, 1929; **73**:51, 1929.

6. Meakins and Davies (footnote 5).

Fluoroscopic observations showed the usual changes in the lung, mediastinal and diaphragmatic shadows following pneumothorax. Lung collapse was less complete and lung expansion was greater in A.G. during respiration than in the other two cases, on account of an adhesion between the lung and the wall of the chest. Mediastinal displacement was also less. Patients F.S. and A.G. showed a "paradoxical" movement of the diaphragm on the affected side after the later insufflations of air. In all cases, there were lowered mean position and decreased mobility of the diaphragm on the affected side.

There was a delayed but distinct rise in the oxygen capacity of the blood of A.G. as pneumothorax progressed. This increase was also reported by Meakins and Davies[6] in their series. The other two patients, D.R. and F.S., were not followed long enough for this change to make itself apparent.

In the serum electrolyte values, which were done on patient D.R., twenty-four hours after his first (900 cc.) pneumothorax, there seemed to be no changes except for a slight general increase in electrolyte concentrations. The significance of this is not clear.

COMMENT

Much work has been done on the problem of the effect of lung collapse on the volume flow of blood through the lungs in animals. For unilateral pneumothorax experiments, rabbits have been found more satisfactory than dogs, on account of the loose, and often perforate, mediastinum in the latter animal. The best of the earlier work on this subject was that of Bruns.[7] This investigator found that after closed unilateral pneumothorax in rabbits, the arterial oxygen saturation was normal or nearly so, and he inferred a decreased blood flow through the collapsed, nonfunctioning lung. Bruns also found that collapse of one lung decreased by about 25 per cent the flow of blood perfused through the pulmonary circuit at constant pressure.

Most of the earlier investigations were reviewed and much careful original work was reported in an article published by Weiss[8] in 1926. After considering all available data, Weiss was able to state definitely that the flow through the collapsed lung, in both open and closed pneumothorax in rabbits, was greatly diminished. The figures on the total blood flow through the pulmonary circuit were somewhat less uniform,

7. Bruns, O.: Ueber den respiratorischen Gaswechsel bei Erkrankungen der Lunge, Deutsches Arch. f. klin. Med. **107**:468, 1912; Ueber die Blutzirkulation in der atelektatischen Lunge, ibid. **108**:469, 1912.

8. Weiss, R.: Ueber die Durchblutung der Kollapslunge beim experimentellen Pneumothorax, Ztschr. f. d. ges. exper. Med. **53**:138, 1926.

but the great majority of these also showed a decrease following pneumothorax.

In man, so far as we are aware, no direct measurement of blood flow before and after pneumothorax has previously been reported. LeBlanc,[9] however, in three of four cases in which the oxygen contents of arterial and of venous blood were measured, found an increase in the arteriovenous oxygen difference.

If, therefore, a decrease in pulmonary blood flow is the rule following lung collapse, the question arises as to the cause of this phenomenon.

There is the possibility that the increase in intrathoracic pressure following pneumothorax may be a cause of a decreased flow of blood into the thorax. That this factor is not a deciding one, however, is convincingly shown by the recent experiments of Moore.[10] This investigator produced lung collapse in dogs by clamping off one main bronchus, with resulting complete atelectasis of that lung. By this technic the intrathoracic negative pressure would tend to be exaggerated rather than reduced. Of six such experiments in which the left bronchus was tied off, five showed a decreased total blood flow, while all of the seven in which the right bronchus was tied showed a decrease.

Whether the displacement of the mediastinum that occurs with lung collapse may produce embarrassment of the heart action and thus a decrease in the cardiac output is a question on which little evidence is available. If such were the case, one would expect an increase in venous blood pressure. This, however, apparently does not occur to an appreciable extent in man. Of two cases measured, Kroetz [11] found one in which the venous pressure increased to about the same extent as the intrathoracic pressure; in other words, the "effective venous pressure" was maintained. In the other case Kroetz found a smaller rise than this in venous pressure. In our case 3, the rise in venous pressure following pneumothorax was insignificant. In experimental pneumothorax, venous pressure changes are apparently a more important factor (Tsunoda [12]).

The chief cause for the decrease in total cardiac output following lung collapse is probably a decrease in the vascular bed and a corresponding increase in resistance in the collapsed lung. The many experiments in animals indicating a marked decrease in blood flow

9. LeBlanc (footnote 5).

10. Moore, R. L.: The Volume of Blood Flow Per Minute Through the Lungs Following Collapse of One Lung by Occlusion of Its Bronchus, Arch. Surg. **22**:225 (Feb.) 1931.

11. Kroetz, C.: Die Koeffizienten des klinisch-messbaren Venendruckes, Deutsches Arch. f. klin. Med. **139**:325, 1922.

12. Tsunoda, H.: Ueber die Ursachen der Venendrucksteigerung bei Pneumothorax, Deutsche Ztschr. f. Chir. **212**:198, 1928.

through the collapsed lung strongly suggest this increase in resistance; the most direct of these experiments are the lung perfusions of the type carried out by Bruns, as quoted. Another phenomenon, noted by Bruns and also by Carlström,[13] that points to an increased resistance in the pulmonary circuit when one lung is collapsed is the hypertrophy of the right ventricle that occurs after long-standing pneumothorax in animals.

If one accepts the statement that the vascular resistance in the collapsed lung is greatly increased, the question arises whether this is due simply to a decrease in size of the vascular bed as a result of the collapse itself, or whether there occurs an active constriction of the pulmonary blood vessels. The perfusion experiments of Bruns, which were carried out on animals' lungs during the half hour immediately after the death of the animal, suggest the former. Other work has confirmed the finding of a progressive decrease in flow through the perfused lung when it is reduced from the expanded to the collapsed state; Daly's[14] recent experiments show this clearly. Further evidence in the same direction is offered by the interesting work of Coryllos and Birnbaum.[15] These investigators found that when iodized oil was injected into the jugular vein of a dog with unilateral lung collapse, the oil particles were of such size that they were caught in the smaller branches of the pulmonary artery. They noted further that the oil particles were distributed about equally between the collapsed and the normal lung. When, however, india ink was similarly injected, the particles penetrated to the pulmonary capillaries, and it was found that the capillaries of the collapsed lung contained considerably less of the particles than those of the normal lung. The authors interpreted this as indicating that the capillaries or alveolar blood vessels were the elements of the pulmonary circuit which were constricted by lung collapse.

The degree to which the flow through the collapsed lung will be reduced, as compared with that through the normal lung, thus depends on the relative resistances along these two parallel circuits. This phase of the problem has been well discussed by Weiss.[8]

There remains the possibility of nonmechanical, vasomotor changes in the pulmonary blood vessels following pneumothorax. On this point we have not found evidence in the literature.

It is perhaps worth noting that if a decreased blood flow is actually the rule after artificial pneumothorax, this phenomenon may well be

13. Carlström, P. G.: Beitrag zur Frage der Wirkung des künstlichen Pneumothorax auf Herz und Zirkulation, Beitr. z. Klin. d. Tuberk. **22**:243, 1912.

14. Daly, I. de B.: Resistance of the Pulmonary Vascular Bed, J. Physiol. **69**:238, 1930.

15. Coryllos, P. N., and Birnbaum, G. L.: The Circulation in the Compressed, Atelectatic and Pneumonic Lung, Arch. Surg. **19**:1346 (Dec.) 1929.

associated with the gradual steady increase in the red blood count and hemoglobin that has been shown to occur.[16]

A further consideration, which so far as we know has not been stressed before, is the fact that this decrease in cardiac output with an increase in peripheral (pulmonary) resistance appears to contradict Starling's "law of the heart," according to which the heart puts out the same volume of blood in spite of wide variations in arterial resistance, providing the venous inflow is constant. Whether there is actually a contradiction here of the law of the heart or whether alterations in venous return, or other circulatory function, are a more immediate cause for the decreased cardiac output is a question that cannot be discussed further with the data available in the present investigation.

Finally, the progressive fall in blood carbon dioxide levels, which occurred in F.S. and A.G., requires explanation. Meakins and Davies,[6] in discussing this phenomenon in their series of cases, brought evidence to show that the carbon dioxide change was associated with the improved pulmonary function that followed the clearing of the infiltrative tuberculous process. In other words, the original carbon dioxide level was high and gradually returned toward normal as the condition of the lung improved. In the case of our two patients, however, this explanation is not satisfactory: 1. There was no carbon dioxide "retention," in the sense that carbon dioxide levels at the beginning were well within normal limits. The arterial serum p_H was also normal. 2. The tuberculous process in the lungs was not very extensive. 3. This process did not show any signs of clearing during the period of observation. 4. The vital capacity and the residual air were both progressively decreasing during the period of observation.

It is of interest to consider the fall of carbon dioxide levels in relation to some of the other changes that have been shown to occur following pneumothorax. As noted, both the vital capacity and the residual air are decreased. More significant than these values, however, from the point of view of the respiratory exchange, is the fact that the "normal capacity" (the volume of air in the lungs at the end of a normal respiration) is also diminished (Anthony and Heine[17]). With a smaller mean lung volume, and the same (or slightly increased) pulmonary ventilation, one would expect a more complete washing out of the alveolar spaces with each respiration and therefore (other things being equal) a lower alveolar carbon dioxide tension and a higher oxygen tension in the alveolar air. If alveolar and arterial carbon dioxide tensions are nearly the same, as they are under normal conditions, it follows that the arterial carbon dioxide content will also be reduced. The state of the

16. Meakins and Davies (footnote 5). Bruns (footnote 7).
17. Anthony and Heine (footnote 5).

circulation, however, is not the same: the total blood flow through the lungs is reduced, and the blood is presumably flowing through a smaller capillary bed. The latter state, in particular, will make proper gas exchange in the lungs more difficult. Whether a decreased circulation rate through the lungs increases or diminishes the efficiency of oxygen and carbon dioxide exchange is not known: the greater time of flow through pulmonary capillaries will provide for a closer equilibrium between blood and lung gases; on the other hand, the pulmonary artery blood will be more "venous" and so require a larger gas exchange for proper arterialization.

In point of fact, the change in pulmonary circulation did not appear to disturb the close equilibrium that exists between alveolar and arterial carbon dioxide tensions, with the result that both alveolar and arterial carbon dioxide levels (owing to more efficient alveolar ventilation) were decreased.

The situation was not the same with regard to oxygen transport in the lungs. The tendency to arterial oxygen unsaturation indicates that in respect to this gas, the pulmonary function was below normal. The difference between the efficiency of carbon dioxide transport and of oxygen transport was very possibly due to the different diffusion rates of these gases through the alveolar membranes. The greater engorgement of the capillary blood vessels in the actively functioning regions of the lungs would be expected to hinder the proper oxygenation of the blood. It is possible also that the arterial unsaturation was due in part to blood flowing through unaerated, or poorly aerated, channels in the lungs. Since, however, other investigators have found normal oxygen saturations after pneumothorax, the effects of the foregoing factors must be quite variable in different cases.

In brief, then, the situation existing after pneumothorax in our cases was one of increased efficiency in carbon dioxide transport by the lungs, together with decreased efficiency in oxygen transport.

From the point of view of the respiratory stimulus, it is interesting that the same, or slightly increased, pulmonary ventilation is maintained in spite of lower arterial carbon dioxide tension and even in one case of increased arterial p_H. The situation here is probably not unlike that described by Kroetz [18] in a certain stage of early cardiac decompensation, in which lowered carbon dioxide tension and increased arterial p_H indicated an uncompensated alkalosis. As Kroetz pointed out, there existed in these cases a definitely decreased arterial oxygen tension, though the percentage of saturation was normal. A similar situation apparently existed in A.G. (case 3); F.S. (case 2) had an actual arterial anoxemia.

18. Kroetz, C.: Formen der Dyspnoe: I. Kardiale Dyspnoe, Deutsches Arch. f. klin. Med. **169**:257, 1930.

SUMMARY

1. Studies of the cardiac output and other functions of the circulation have been made before and after artificial pneumothorax in three cases of pulmonary tuberculosis.

2. The cardiac output was decreased following pneumothorax in all cases. Among the other changes that occurred were: decreased vital capacity and residual air and lowered alveolar and blood carbon dioxide levels. The interrelations of some of these changes are discussed.

REPORT OF CASES

CASE 1.—*History.*—D. R. (no. 80552), a boy, aged 17, was first admitted to Bellevue Hospital on Aug. 28, 1928, with a five months' history of cough and night sweats and a loss of 10 pounds (4.5 Kg.) in weight.

Examination.—Examination at this time showed signs of infiltration throughout the upper lobe of the left lung. The sputum was positive for tubercle bacilli. During the next four months, he improved clinically, but the process in the lungs extended somewhat and a cavity formed at the apex of the left lung. His weight in September, 1928, was 118 pounds (53.5 Kg.), and on March 16, 1929, was 132 pounds (59.9 Kg.). He was transferred to the Presbyterian Hospital on March 20.

Examination of the blood showed: hemoglobin, 82 per cent (Sahli); red cells, 4,670,000; white cells, 14,500; polymorphonuclears, 66 per cent; lymphocytes, 29 per cent; monocytes, 4 per cent; basophils, 1 per cent. The urine was normal.

An electrocardiogram gave normal tracings. A roentgenogram showed infiltration extending into the apexes of both lungs, with a cavity in the left.

Course.—The patient was comfortable and practically free from symptoms throughout his stay, except for those due to pneumothorax. Nine hundred cubic centimeters of air was injected by Dr. Amberson on April 1, following which the pulse rate rose to 120, and there were dyspnea and a transient cyanosis lasting about two hours. The second and third insufflations were followed by tachycardia and an increased respiratory rate, but no cyanosis. Roentgenograms and fluoroscopy showed no evidence of adhesions of the left lung to the chest wall. The heart was markedly displaced to the right. The patient was transferred to Bellevue Hospital on April 9.

CASE 2.—*History.*—F. S. (no. 239168), a white man, aged 24, was admitted to the hospital on Dec. 30, 1929, complaining of cough, transient pains in the right side of the chest and loss of weight for five months. He had had a few night sweats. He had lost 25 pounds (11.3 Kg.), and the present weight was 105 pounds (47.6 Kg.). He had been at Bellevue Hospital for seven weeks before admission, where moderate tuberculous infiltration and excavation had been found. A week before, he had received a small artificial pneumothorax (150 cc.).

Examination.—Examination showed a pale, undernourished young man with a frequent cough of varying severity, bringing up mucopurulent sputum. The trachea was in the midline. There were deep supraclavicular fossae. The lung expansion was good; the chest was symmetrical. There was dulness over the right apex, with bronchovesicular breath sounds and many moist râles after coughing. The heart was normal; the apex was 8 cm. to the left in the fifth space. The blood pressure was 95 systolic and 70 diastolic.

Examination of the blood showed: hemoglobin, 89 per cent (Sahli); red cells, 4,500,000; white cells, 10,280; polymorphonuclears, 73 per cent; lymphocytes, 21 per cent; monocytes, 5 per cent; eosinophils, 1 per cent. The red cells showed central pallor. The sputum contained tubercle bacilli on several occasions.

A roentgenogram of the chest taken Dec. 30, 1929, showed a dense process through the upper lobe of the right lung, with a large cavity 3 cm. in diameter in the right infraclavicular region. The diaphragm appeared normal.

Course.—During the patient's stay of one month in the hospital, he had a low fever most of the time, about 100 F.; during the week from Jan. 9 to 15, 1930, the afternoon rise was as high as from 101 to 102 F. He was relatively comfortable; he was bothered at times by coughing in the night; he had an irregular appetite, and there was a good deal of diaphoresis. Following the first pneumothorax, on January 21, there were a transient rise of the pulse rate to 130 and slight dyspnea, which subsided in a few hours. There was a mild cyanosis of the nail beds, which nearly cleared after two days. Subjectively, the patient had a sensation of tightness in his chest. The symptoms after the succeeding injections of air were similar but less marked, except that cyanosis of the nail beds persisted, the respiration became shallow and slightly increased in rate, and he noticed his heart beating against the chest wall on the left side. On January 28, the right border of cardiac dulness in the fourth space was 3.5 cm. to the left of the midline. It was observed that after slight exertion the patient became more cyanosed. Roentgen examination of the chest on January 27 showed the right lung to be collapsing freely, except for adhesions just beneath the clavicle. Fluoroscopy showed that the collapsed lung did not move appreciably with respiration. The patient was transferred back to Bellevue Hospital on February 1.

Case 3.—*History.*—A. G. (no. 287218), a Russian-born Jewish boy, aged 20, was admitted to the hospital on Feb. 17, 1931, complaining of cough, hemoptyses and loss of weight during the preceding five months. He had worked as a shoe salesman for the past three years, being in a poorly lighted, damp basement. A brother had active tuberculosis. There had been no important previous illnesses.

Five months before admission, he caught a severe chest cold; cough developed, with sputum that became blood-streaked. The patient was in Queensboro Hospital for two weeks; a roentgenogram taken there was negative. He went home and rested for three weeks, and then returned to work. He soon lost his appetite, and his weight dropped from 132 to 117 pounds (59.9 to 53.1 Kg.). Nine weeks before admission, the cough returned and he had two hemoptyses of from 100 to 200 cc. The sputum increased, and he had night sweats. He stayed in bed at home for a month, and then went to Bellevue Hospital. A moderately advanced exudative tuberculous lesion was found in the left lung above the third rib. On February 14, a small pneumothorax of 150 cc. was given on the right side. The patient was then transferred to the Presbyterian Hospital for study.

Examination.—Examination showed a somewhat undernourished Jewish boy who appeared chronically, but not seriously, ill. The lungs showed dulness, diminished breath sounds and increased whispered voice over the upper lobe of the right lung posteriorly, and below the clavicle anteriorly. There were moist râles in this region.

Examination of the blood showed: hemoglobin, 78 per cent; red cells, 4,920,000; white cells, 14,600; polymorphonuclears, 78 per cent; Wassermann reaction, negative. Urinalysis gave negative results. Tubercle bacilli were found in two of four sputum examinations.

Roentgenograms of the chest showed mottled infiltration involving the apex of the right lung and the first and second interspaces. Subsequent roentgenograms showed the production of a partial pneumothorax, with adhesion to the chest wall at the level of the second interspace. A small (1.5 cm.) cavity in this region was visualized. A little fluid collected in the costovertebral angle.

Course.—The patient's general condition remained about the same. He had a low fever at times. Pneumothorax was started on March 4 and was given twice a week, 4,750 cc. of air being injected in the course of five weeks. The pulse rate increased, the pulmonary ventilation increased slightly, and the vital capacity fell from 4,100 to 3,100 cc. during this time. Fluoroscopy showed partial collapse, but the lung still moved somewhat during quiet respiration. Subjectively, the patient felt fairly well; there was no pain in the chest.

The patient had a small intestinal hemorrhage (hemorrhoids?) on March 20. On March 30, he had some discomfort in the right ear; he was found to have a low grade infection of the middle ear and maxillary sinusitis. He was transferred to Bellevue Hospital again on April 8, 1931.

PANCREATIC EXTRACT IN THE TREATMENT OF ANGINA PECTORIS AND INTERMITTENT CLAUDICATION

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Much experimental and pathologic evidence has accumulated to indicate that the pain of angina pectoris is due to disturbance of the coronary circulation. The ideal therapeutic measure, then, would be one that insures at all times an adequate flow through the coronary arteries. Of the various drugs used in the treatment of this disease, those which are known to dilate the coronary arteries have received the widest acceptance. For relief from the attack, the nitrites are invaluable, not only because they reduce the systemic blood pressure and thus relieve in part the burden imposed on the heart muscle, but also because in all probability they decrease myocardial ischemia. Unfortunately, their effect is transitory. For the prevention of attacks, another class of drugs which act in much the same manner, namely, the purine derivatives (theobromine, theophylline, etc.) have proved of value. However, these drugs fall short of the ideal because they are often badly borne by the patient and because a tolerance to them is quickly acquired.

In this paper we wish to summarize our experience with a new preparation, an insulin-free extract of the pancreas. It is well tolerated in large doses. It is an active coronary dilator with a prolonged effect. In many instances it will prevent attacks of angina pectoris that recur after the usual methods of treatment. We have furthermore found it superior to other measures in the treatment of intermittent claudication.

It was originally noted,[1] several years ago, that the pain of angina pectoris was sometimes relieved by insulin in diabetic patients with this syndrome. The degree of relief was apparently not dependent on the amount of insulin used. It remained for Gley and Kisthinios[2] to

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1. Heteny and Budinger, cited by Vaquez, Giroux and Kisthinios, Presse méd. **37**:1277 (Oct. 2) 1929.

2. Gley, P., and Kisthinios, N.: Recherches sur la substance hypotensive de pancréas, Presse méd. **37**:1279 (Oct. 2) 1929.

demonstrate that the effective material was not insulin, but another substance present in the pancreas. They succeeded in making an insulin-free pancreatic extract, which Vaquez [3] used in the treatment of angina pectoris and spastic obliterative arterial disease with remarkable results. In 1929 he reported a series of twenty cases of severe anginoid seizures in which from partial to complete amelioration of symptoms resulted from the treatment in almost every instance. Similar results were obtained in the treatment of intermittent claudication. The duration of relief was variable, but in several instances no symptoms recurred after prolonged observation. He concluded that this therapy was far superior to any surgical measure.

Wolffe and his co-workers,[4] in this country reported similarly favorable results from this method of treatment. In a series of twenty instances, complete relief from anginoid seizures was obtained in 55 per cent; 30 per cent of the patients were partially relieved, and three, or 15 per cent, experienced no relief. Two of the latter showed decompensation at the time that treatment was given; as the author remarked, Vaquez had observed complete failure in such instances.

PHARMACOLOGIC PROPERTIES

Pharmacologic studies, together with the method of preparation of the extract, have been reported elsewhere.[5] The pertinent observations may be summarized at this time.

The pancreatic extract, on intravenous injection into the rabbit, causes a transitory hypotension which is not the result of cardiac slowing and is not due to peptones, choline or histamine. The "hypotensive unit," as defined by Gley and Kisthinios, has been adopted. It is that amount of the extract injected intravenously which is sufficient to cause a barely perceptible fall in the blood pressure of a rabbit weighing 2 Kg. Repeated injection of the unit dose, or continuous intravenous perfusion in an approximate dose of 0.002 hypotensive unit per kilogram per minute may result in a prolonged hypotension from cumulative action. The extract causes vasoconstriction of the vessels of a perfused rabbit's leg; hence the hypotension is probably due to splanchnic vasodilatation.

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3. Vaquez, H.; Giroux, R., and Kisthinios, N.: De l'action de certains extraits pancréatique dans le traitement de l'angine de poitrine, Presse méd. **37**: 1277 (Oct. 2) 1929.

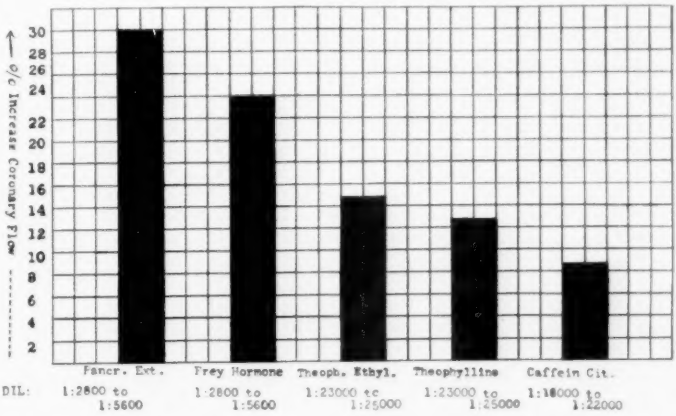
4. Wolffe, J. B.; Findlay, D., and Dessen, E.: Treatment of Angina Pectoris with a Tissue Vasodilator Extract, Ann. Int. Med. **5**:625 (Nov.) 1931.

5. Elliot, A. H., and Nuzum, F. R.: The Pharmacologic Properties of an Insulin-Free Extract of Pancreas and the Circulatory Hormone of Frey, J. Pharmacol. & Exper. Therap. **43**:463 (Nov.) 1931.

The pressor effect of epinephrine may be modified or abolished by the extract. As noted by its elaborators, the extract protects the experimental animal from lethal doses of epinephrine. It does not, however, modify the action of epinephrine on the carbohydrate metabolism; it modifies only its action on smooth muscle.

None of these effects was obtained after subcutaneous or intramuscular injection of the extract.

Using the perfused rabbit's heart, we found that the extract in dilutions corresponding to the therapeutic dose in man is an active coronary dilator. The degree of coronary dilatation exceeded by one-half that obtained with the most active of the purine group in this respect, theophylline ethylenediamine.



Effect of pancreatic extract, Frey hormone, theophylline ethylenediamine, theophylline and citrated caffeine on the coronary flow of the perfused rabbit's heart. The vertical scale at the left indicates the increase in coronary flow in per cent.

The results are expressed graphically in the accompanying chart. The height of each column indicates the average increase in coronary flow as determined in from five to ten experiments conducted over a period of ten minutes on fresh hearts. Pancreatic extract caused an average increase of 30 per cent; the Frey "hormone," as prepared from the urine, an increase of 24 per cent. The purine derivatives, theophylline ethylenediamine, theophylline and caffeine, were less effective, producing increases of 15 per cent, 13 per cent and 9 per cent, respectively.

The effects of the intravenous injection of the extract into man were studied in a few instances. With a dosage of 30 hypotensive units, patients with hypertension experienced an immediate transitory, "nitrite"

reaction (flushing of the face, vertigo, faintness and palpitation) and a pronounced fall of systolic blood pressure, together with tachycardia which persisted for about one hour. No changes were apparent in the electrocardiogram taken during and following the injection. In persons with normal blood pressure, little or no effect was noted. Although no untoward reactions occurred, the number of these observations was limited. It is not recommended that the extract be given intravenously without further study.

NATURE OF THE ACTIVE PRINCIPLE

The exact nature of the active principle remains obscure. Because of similarity in physiologic properties, Wolffe suggested that we might be dealing with an adenine compound. Drury and Szent-Györgyi [6] and Wedd [7] recently studied the properties of a substance prepared from extracts of heart muscle and identified as an adenine compound, probably adenylic acid. Among other effects, adenylic acid and related compounds cause a transitory fall in blood pressure in the experimental animal, an increase in the coronary flow of the perfused rabbit's heart exceeding that produced by sodium nitrite and theophylline and transitory complete heart-block in the guinea-pig. The latter effect is regarded as specific for these compounds. We have been unable to produce it

Another principle regarded as a hormone, and having closely allied with the pancreatic extract, and so are doubtful of the identity of these principles.

properties, has been described. Frey and his co-workers [8] isolated in fairly pure form a substance present in the urine of normal persons and animals that on intravenous injection into the dog causes hypotension

6. Drury, A. M., and Szent-Györgyi: Physiological Activity of Adenine Compounds with Special Reference to Their Action on the Mammalian Heart, J. Physiol. **68**:213 (Nov.) 1929.

7. Wedd, A. M.: The Action of Adenosine and Certain Related Compounds on the Coronary Flow of the Perfused Heart of the Rabbit, J. Pharmacol. & Exper. Therap. **41**:355 (March) 1931.

8. Frey, E. K., and Kraut, H.: Ein neues Kreislaufhormon und seine Wirkung, Arch. f. exper. Path. u. Pharmacol. **133**:1, 1928. Kraut, H.; Frey, E. K., and Bauer, E.: Ueber ein neues Kreislaufhormon, Ztschr. f. phys. Chem. **175**:97, 1928. Frey, E. K., and Kraut, H.: Nachweis und Wirkung eines Kreislaufhormon, München. med. Wchnschr. **75**:763 (May 4) 1928. Frey, E. K.: Kreislaufhormon und innere Sekretion, München. med. Wchnschr. **76**:1951 (Nov. 22) 1929. Kraut, H.; Frey, E. K., and Werle, E.: Der Nachweis eines Kreislaufhormon in der Pankreasdrüse, Ztschr. f. phys. Chem. **189**:97, 1930. Frey, E. K.: A New Internal Secretion of the Pancreas, quoted in Foreign Letters, J. A. M. A. **95**:676 (Aug. 30) 1930. Frey, E. K.; Kraut, H., and Schultz, F.: Ueber eine neue innersekretorische Funktion der Pankreas, Arch. f. exper. Path. u. Pharmakol. **158**:334, 1930.

and an increase in cardiac rate and amplitude of contraction. This substance is present in the blood stream in combination with an inactivator from which it may be liberated. Frey believes that it is present in most organ extracts but is probably elaborated by the pancreas, because after experimental pancreatectomy the rate of urinary excretion is decreased 80 per cent or more. The linkage between the hormone and inactivator depends on the reaction of the tissues, so that the appearance of "acid metabolism" releases a portion of the hormone, resulting in its vasodilator action.

The hormone has been used clinically with, for the most part, favorable results. Frey stated that as the result of its use he has seen lowering of the blood pressure in essential hypertension, cessation of attacks of angina pectoris and intermittent claudication and avoidance of amputation in gangrene of the extremities resulting from arterial disease. Leschke,[9] using this preparation, obtained gratifying results in all manner of angiospastic syndromes including angina pectoris, and believes that it is the treatment of choice in arteriosclerotic gangrene and thrombo-angiitis obliterans. He obtained identical results with the insulin-free pancreatic extract. Schauder[10] described a patient with severe intermittent claudication of a year's duration who, as the result of treatment with the hormone, had remained entirely symptomless following treatment for a period of thirteen months. The patient also had hypertension, and a pronounced and lasting fall in blood pressure resulted.

On the other hand, Singer[11] had no success with either the "circulatory hormone" or the pancreatic extract in these conditions, and attributed the favorable results reported by others to a nonspecific protein effect.

Extracts of other tissues, namely, heart, liver and skeletal muscle, have been found to exert a beneficial effect on the anginal syndrome. Haberlandt,[12] in 1924, found that an extract made from the cardiac conduction system had the ability of initiating and regulating the beat of an isolated heart perfused with it. He believed it to be a "heart hormone." Salomon and Zuelzer[13] found a similar principle in an

9. Leschke, E.: Erfahrungen mit dem Kreislaufhormon "Kallikrein," München. med. Wchnschr. **77**:1167 (June 22) 1930.

10. Schauder, H.: Zur Behandlung der intermittierenden Hinkens, München. med. Wchnschr. **77**:485 (March 21) 1930.

11. Singer, R.: Die praktischen Ergebnisse der "Herz Hormon" Therapie, Wien. klin. Wchnschr. **46**:39 (Jan. 9) 1931.

12. Haberlandt, L.: Ueber das Herzhormon, Endokrinologie **6**:335 (May) 1930.

13. Salomon, H., and Zuelzer, G.: Ueber das aus der Leber gewonnene Herzhormon "Eutonon," Ztschr. f. d. ges. exper. Med. **66**:291, 1929.

extract of liver. These two preparations, together with a skeletal muscle extract introduced by Schwarzmann,[14] are regarded by their elaborators as of distinct benefit in the treatment for angina pectoris. Haberlandt believes that the skeletal muscle extract of Schwarzmann contains a substance identical with his "heart hormone." Fahrenkamp and Schneider[15] came to a similar conclusion. They compared the effects of these two preparations on patients with angina pectoris. The results were identical, the angina being favorably influenced.

We have not had the opportunity of studying these preparations. However, in conjunction with the studies on the pharmacology of the pancreatic extract, we conducted parallel observations on the "circulatory hormone" of Frey as prepared from the urine. It was found to have similar vasodilator properties, and, in addition, it modifies the pressor effects of epinephrine and is an active coronary dilator. On the strength of these observations, it may be concluded that these two preparations probably contain the same active principle.

From this review it is evident that a substance or substances have been found in various animal tissues and fluids that have similar physiologic properties. Whether the active principles are identical or represent a class of substances or a hormone is not known at this time. It is striking, however, that these investigators, working independently, have observed a salutary influence exerted by their preparations on the symptoms and course of spastic and obliterative arterial disease as typified by angina pectoris, intermittent claudication, arterial hypertension and trophic disturbances of the extremities.

CLINICAL STUDIES

Dosage.—We administered the extract intramuscularly in doses of from 30 to 60 hypotensive units on alternate days or twice weekly, depending on the severity of the symptoms, for a total of from ten to twelve doses. This procedure was followed in both angina pectoris and intermittent claudication. If amelioration of symptoms was not apparent after such a course, the injections were repeated after a week's interval. In refractory cases, a third such course was given before it was concluded that the treatment was without avail. Frequently, anginal attacks ceased after from four to five injections. If symptoms recurred after weeks or months, the treatment was repeated if possible. Toxic symptoms or side reactions were not noted during or after repeated

14. Schwarzmann, J. S.: Ein neuer Weg in der Therapie der Angina pectoris, München. med. Wchnschr. **76**:1329 (Aug. 9) 1929.

15. Fahrenkamp, K., and Schneider, H.: Vergleichende Untersuchungen mit einem als "Hormocardiol" bezeichneten Herzhormonpräparat und einem neuartigen Muskelextrakt, Med. Klin. **26**:48 (Jan. 10) 1930.

series of injections. Burning and slight induration were often encountered at the site of injection.

Careful attention has been paid to the potency of the material used. During the early months we prepared our own extract. Later it was supplied by two commercial houses. Each lot was tested on the rabbit and the dosage was determined on that basis. We also tested material on the perfused heart to assure ourselves that the coronary dilator principle was active. Frequently a discrepancy was encountered between this and the vasodilator property of the extract. This may have been due to a trace of choline or histamine, which are coronary constrictors. Only that material was used which actively dilated the coronary arteries.

Selection of Cases.—Three groups of patients were studied. The first group comprised forty-one persons with angina pectoris who received the usual treatment, namely, limitation of activity, the use of nitrites and nitroglycerin when effective and various combinations of the purine derivatives, together with such drugs as phenobarbital, atropine, a mixture of opium alkaloids, etc. A diminution of tobacco consumption was insisted on. This group served as a control.

The second series consisted of twenty patients with angina treated with the pancreatic extract. Many of these had previously had the benefit of other methods of therapy.

The third group numbered five persons with intermittent claudication and two with other types of arterial disease.

All of these patients were seen in private practice. No attempt at selection was made beyond the reasonable certainty of diagnosis and the elimination of patients with coronary thrombosis. Patients with syphilitic aortitis were not excluded, as Vaquez had obtained relief with the treatment in such instances. Orthodiagraphic heart measurements and electrocardiograms were made on each patient. The follow-up period was of sufficient length to admit of accurate evaluation of the therapeutic measures employed.

For purposes of comparison, the control and treated groups of angina patients were divided into three subgroups each, depending on the severity of the disease. As the criteria for this division, the limitation of physical and emotional activity and the duration and severity of the attacks were considered.

The control group was followed for an average period of twenty and four-tenths months. Nineteen patients had hypertrophied hearts, as determined by the orthodiagram, and twelve of these had hypertension. Definite electrocardiographic evidence of myocardial damage was present in thirteen, or 31.7 per cent, of the group. The urinalyses gave uniformly negative results. Two positive Wassermann reactions were encountered in the group. The first patient had a syphilitic aortitis

and received pronounced benefit from antisyphilitic medication. The second patient, 70 years of age, had a 2 plus Wassermann reaction of the blood, and was helped by potassium iodide. The duration of symptoms varied from one week to one hundred and eighty months at the time that treatment was instituted, averaging twenty-four and four-tenths months.

Results of Treatment.—The salient facts are presented in table 1. Three of these patients were classified as having slight attacks; one of them received no relief from treatment; one was moderately benefited, and one markedly relieved. Of the twenty patients with attacks of moderate severity, four experienced no relief, seven were moderately benefited and nine showed pronounced improvement. Eighteen patients had a severe form of the disease. Five of these were unrelieved by

TABLE 1.—*Results in Forty-One Patients with Angina Pectoris, Treated by the Usual Measures*

Severity of Attacks	Number of Cases	Duration of Symptoms	Average Time Observed, Mo.	Coronary Disease (Electrocardiogram)		Degree of Relief						Died	
						None		Moderate		Marked			
				No.	%	No.	%	No.	%	No.	%	No.	%
Slight	3	1 wk to 17 mo. (av. 5 mo.)	17.6	1	33	1	33	1	33	1	33	..	....
Moderate	20	3 to 144 mo. (av. 36.4 mo.)	20.9	6	30	4	20	7	35	9	45	..	....
Severe	18	1 wk. to 180 mo. (av. 32 mo.)	22.8	6	33	5	27.7	6	33	4	22.2	3	16.6
Totals	41	Av. 24.4 mo.	20.4	13	31.7	10	24.3	14	34.1	14	34.1	3	7.4

treatment. Six were somewhat relieved and four were benefited greatly. Three of the eighteen patients died during the period of observation.

In summary, of the total group of forty-one control patients, ten, or 24.3 per cent, were not helped by treatment; fourteen, or 34.1 per cent, experienced moderate relief, and fourteen, or 31.7 per cent, received pronounced benefit. Three patients, or 7.4 per cent, died during observation.

The group of twenty patients treated with pancreatic extract presents a similar cross-section. Eleven had hypertrophied hearts, and there was electrocardiographic evidence of myocardial damage in twelve, or 60 per cent. Ten had hypertension, of whom one had a mild diabetes mellitus and one a chronic nephritis. No evidence of syphilis was encountered in this group.

The duration of symptoms when first seen (average, twenty-three and three-tenths months) was similar to that in the control group, varying from one week to eight years. At least 50 per cent of these patients

had been treated by the usual methods without appreciable benefit before the extract was given. This enhances the significance of the satisfactory results obtained in these instances.

Each patient received from 120 to 1,140 hypotensive units (average for the group, 517.5 units). During the treatment with the extract, other methods of therapy previously instituted were, in most instances, interrupted. A few patients continued to take vasodilator drugs for relief from attacks during the time that the first few injections of the extract were administered. After the completion of the course these drugs were stopped, except in two instances in which the extract was ineffective. Every patient has been followed to the present time. The shortest period of observation following treatment was one month, the longest twenty-two months and the average for the group nine and five-tenths months.

TABLE 2.—*Results in Twenty Patients Treated with Pancreatic Extract*

Severity of Attacks	Number of Cases	Duration of Symptoms	Average Time Observed, Mo.	Coronary Disease (Electrocardiogram) No.	Coronary Disease (Electrocardiogram) %	Number Hypotensive Units Given	Degree of Relief: None No.	None %	Moderate No.	Moderate %	Marked No.	Marked %	Died No.	Died %
Slight	2	1 wk.; 18 mo.	14.0	..	....	120; 585 (av. 352)	..	....	1	50	1	50	..	....
Moderate	8	1 to 48 mo. (av. 20.3 mo.)	13.0	5	62.5	100 to 570 (av. 362.5)	1	12.5	3	37.5	4	50	..	....
Severe	10	1.5 to 96 mo. (av. 31.7 mo.)	24.2	7	70	210 to 1,140 (av. 838.0)	1	10.0	1	10.0	6	60	2	20.0
Totals	20	Av. 23.3 mo.	17.0	12	60	Av. 517.5	2	10.0	5	25.0	11	55	2	10.0

The results of treatment are given in table 2. Two of the twenty patients were considered as having attacks of mild severity. One of these was moderately helped, and the other received pronounced benefit. The attacks were moderately severe in eight patients, and five of these had electrocardiographic signs of myocardial damage. In one the attacks proved refractory, three were moderately helped by the extract and four were almost entirely relieved.

The group of ten patients with severe angina is of particular interest. Seven of them had pronounced myocardial damage as evidenced by the electrocardiographic tracings. Their average duration of symptoms was thirty-one and seven-tenths months at the time that treatment was instituted, and they received an average of 838 units each. One patient was not benefited, one was moderately improved and six showed pronounced benefit. Two patients of this group treated with pancreatic extract died suddenly during observation. Necropsy was not possible, but coronary occlusion was suspected. One of these patients, a woman aged 54, while in the hospital had repeated severe nocturnal attacks of

angina pectoris and cardiac asthma; these were so benefited by the extract that she was able to return to her household duties without further precordial distress until death supervened four months later. The other patient, a man aged 71, who had hypertension and diabetes mellitus, when first seen could not walk two blocks without precordial oppression. He was symptomatically relieved after twelve injections until death four months later.

Two patients were not helped by the extract. One had congestive heart failure at the time that treatment was given. Vaquez and Wolffe have likewise experienced failure under these circumstances. The other patient, a man aged 65, who had a blood pressure of 210 systolic and 90 diastolic and a severe angina of six weeks' duration, was unimproved after 1,080 units and rest in bed for one month.

Of the twenty patients, then, two (10 per cent) were not helped, five (25 per cent) were somewhat relieved and eleven (55 per cent) were greatly helped, while two, who experienced benefit from the treatment, died.

The duration of the benefit received from the injections is difficult of evaluation. As mentioned, all of the patients have been followed to the present time. The treated group has fared decidedly better than the control group. We do not wish to ascribe this result entirely to this method of treatment. A necessary part of the program has been to teach the patient to adjust his life to the restrictions imposed on his activity by his disease so that he may be enabled, so far as possible, to avoid those things which precipitate an anginal seizure. However, the patients in the control series received fully as much consideration in this regard, yet the improvement has not been so lasting as that of the treated group. It is possible that our facility in the general management of patients with angina may have improved since we treated the control group of patients, but it seems unlikely that this factor is in itself sufficient to explain the results obtained in the group receiving the pancreatic extract.

The blood pressure was not significantly altered in the patients with hypertension. Kervarec and Enachesco[16] reported favorable results in fifty-two patients with hypertension treated with the extract. Lowering of blood pressure, particularly in instances of essential hypertension, became evident after three or four injections and persisted for as long as seven months. We were unable to confirm these results.

Intermittent Claudication.—Five patients with this syndrome have been treated with the extract. The same dosage was used as in the treatment for angina pectoris. The results have been exceedingly

16. Kervarec and Enachesco: The Effect of Insulin-Free Pancreas Extract in Arterial Hypertension, Progrès méd. **58**:194, 1930.

gratifying. No case has proved entirely refractory. One of these patients also had angina pectoris. Following a course of 1,140 units, the anginal attacks materially lessened in number and severity, and the patient was able to walk comfortably four times as far as he could previous to treatment.

Three of these patients had calcareous changes in the leg vessels as shown by roentgenograms. One had discoloration and burning of the feet and extreme pain in the calves on walking. This patient was so improved after 140 hypotensive units that he returned to his work as janitor. The cyanosis of the feet was not influenced, however. The most satisfactory result was obtained in a patient, 76 years of age, who could not walk one block without pain in the legs. Following a course of 900 units, he could walk for two miles without discomfort. This improvement has been maintained over a three months' period.

One patient with an early thrombo-angiitis obliterans of the extremities was studied. A Mexican, aged 39, when first seen was wearing felt pads in his shoes because of almost constant pain and tenderness in the balls of the toes, which at times extended into the calves of the legs. Sleep was impossible because of the pain, and the patient was exhausted. He used tobacco to excess. Nothing of moment was found on examination except pallor of the toes. No arterial changes were evident in the roentgenogram. After a course of 330 hypotensive units the patient slept the night through and could walk twelve blocks without distress. The color of the toes was improved.

Another patient, 87 years of age, with generalized arteriosclerosis but a normal blood pressure, had mild, intermittent attacks of precordial distress, and on two occasions repeated attacks of numbness and tingling of the right arm and right side of the face, unilateral muscular weakness and difficulty of speech. On the first occasion the symptoms disappeared following five injections of the extract. They recurred six months later. The extract was immediately administered, and the patient promptly became symptomless and has remained so (four months). The symptoms in this instance were probably due to spasm of the cereberal vessels. Their disappearance might have been coincidental, but relief was so immediate and lasting that we have attributed it to the effect of the extract.

CONCLUSIONS

The efficacy of a therapeutic measure in a disease such as angina pectoris, with its variability of symptomatology and scarcity of objective findings, should be judged with extreme caution. We have attempted to present our material without prejudice, and urge the reader to draw his own conclusions.

It is our belief that in this series of patients the benefits from this method of treatment have exceeded those obtained by the usual methods. The results were particularly gratifying in intermittent claudication, a disease notoriously refractory to therapeutic endeavor. We do not know the duration of benefit, nor are we certain that the proper dosage and injection intervals have been used to insure maximum effects. Our

number of observations has been comparatively limited. Since, however, a definite trend is evident even in this small group of observations, and since the treatment is without harmful effects and is both simply and expediently given, a wider use of the method is warranted to establish its ultimate worth.

SUMMARY

An insulin-free extract of the pancreas, a vasodilator that modifies the pressor effects of epinephrine and dilates the coronary arteries of the rabbit's heart to a degree exceeding that produced by drugs of the purine group, was administered intramuscularly to twenty patients with angina pectoris. Two, or 10 per cent, were not helped; five, or 25 per cent, were somewhat relieved; eleven, or 55 per cent, were greatly helped, and two who were benefited by treatment died later.

Forty-one patients with angina pectoris who received the usual medical treatment and were followed for a like period of time were studied as a control series. In ten instances, or 24.3 per cent, no benefit was observed; fourteen patients, or 34.1 per cent, experienced moderate relief; fourteen, or 34.1 per cent, received pronounced benefit, and three, or 7.4 per cent, died.

Five patients with intermittent claudication, one with thromboangiitis obliterans and one with cerebral vascular spasms and angina pectoris were benefited in a pronounced degree by treatment with the extract.

SOME FACTORS DETERMINING THE INSENSIBLE PERSPIRATION OF MAN

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The insensible perspiration has long been a matter of scientific curiosity, for as far back as 1614 it was the subject of investigation by Sanctorius [1] in what were probably among the first quantitative measurements of human metabolism. The number of papers that have dealt with insensible perspiration within the last few years indicates a revival of interest in it, a renewed endeavor to interpret its physiologic significance and an attempt to explore the possibilities of its clinical application. Experiments have shown that most of the loss in weight (85 per cent) of the human body by insensible perspiration is due to the evaporation of water from the respiratory surfaces and from the skin,[2] and that within certain limits approximately 25 per cent [3] of the total heat lost from the human body is abstracted by the evaporation of water from its surfaces.[4] On these facts has been based the application of measurements of insensible perspiration to the study of energy metabolism.

The unique design of the balance employed by Lombard [5] made it possible to measure the insensible loss in body weight of a man within a few minutes with great accuracy, although the skill required for its

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1. Sanctorius: Medicina Statica, translated by John Quincy, ed. 2, London, W. & J. Newton, 1720.

2. Benedict, F. G., and Benedict, C. G. Perspiratio insensibilis: Ihr Wesen und ihre Ursachen, Biochem. Ztschr. **186**:278, 1927.

3. Obviously if visible or sensible (as opposed to insensible) perspiration enters as a factor, the proportion of heat lost from the body by evaporation of water will be increased.

4. Benedict, F. G., and Carpenter, T. M.: The Metabolism and Energy Transformations of Healthy Men During Rest, publ. 126, Carnegie Inst. Washington, 1910, pp. 197 and 241. Soderstrom, G. F., and Du Bois, E. F.: The Water Elimination Through Skin and Respiratory Passages in Health and Disease, Arch. Int. Med. **19**: 931 (May) 1917.

5. Lombard, W. P.: A Method of Recording Changes in Body Weight Which Occur Within Short Intervals of Time, J. A. M. A. **47**:1790 (Dec. 1) 1906.

use was such as to render it unsuitable for general requirements. In the meantime a balance capable of weighing 100 Kg. with a sensitivity of 0.1 Gm. was placed on the market by Sauter of Ebingen, Würtemberg, Germany. With this type of balance short period determinations of the insensible perspiration were first made with human beings by the Nutrition Laboratory in 1910.[6] Subsequently, the Sauter balance was used to study the relations between the basal metabolism and the insensible perspiration in a number of normal and pathologic subjects,[7] and shortly thereafter simultaneous measurements were made of the insensible perspiration and the respiratory metabolism with the special object of noting the proportions of the insensible perspiration derived from the skin and the lungs, respectively.[2] These measurements indicated that the basal metabolism is proportional to the insensible perspiration. Indeed, a straight line curve has been published [7] to represent the relationship between the insensible perspiration and the metabolism.

The plans and the results of some of the experiments on insensible loss that have been reported recently indicate that some investigators have not fully sensed the precautions necessary for the successful application of insensible perspiration measurements to physiologic and clinical problems. The procedures by which such determinations have been made during the past few years may be divided into two groups. According to one procedure, the insensible loss in weight of the subject is measured with an accuracy of about 10 Gm., but is observed over a long period, usually overnight. This kind of measurement has undoubtedly a considerable range of usefulness, particularly for clinical purposes, and its possibilities have already been demonstrated.[7] A second procedure is to employ a sensitive balance for measurements of the changes in body weight occurring in several short (fifteen minute), consecutive periods. The present discussion is limited to this latter type of experiment. In those instances in which the basal metabolism cannot be determined directly by the ordinary methods, these short period measurements have a practical utility because of the ease, the rapidity and the absence of interference with the subject with which they can be made. But the sensitivity (1 : 1,000,000 that is, 100 Kg. : 0.1 Gm.) of the balance used imposes a limitation difficult to overcome. It is impracticable to avoid completely the use of hygroscopic textiles for the clothing and the covering of the subject during the period of measurement. Because of the avidity with which these materials take up water from the atmosphere of average humidity, one cannot assume that these

6. Benedict, F. G., and Carpenter, T. M.: Respiration Calorimeters for Studying the Respiratory Exchange and Energy Transformations of Man, publ. 123, Carnegie Inst. Washington, 1910, figs. 4 and 9.

7. Benedict, F. G., and Root, H. F.: Insensible Perspiration: Its Relation to Human Physiology and Pathology, Arch. Int. Med. **38**:1 (July) 1926.

textiles have a constant weight except under conditions of unchanging humidity of the atmosphere in which the weighings are made. The extremes that can occur in variations in weight due to this factor have been well shown by Heller.[8] He found that the apparent weight of a spring mattress stretched on a wooden frame, covered with a tick, and provided with standard hospital bed covering, underwent an extreme variation of 559.9 Gm. during the course of a number of weighings extending over a period of approximately one month. Rates of variation of as much as 8.3 Gm. per hour were observed. Variations of this magnitude might introduce serious errors even into short period experiments and yield ridiculous results in long period experiments. It is not at all unlikely, as Heller pointed out,[8] that some of the contradictory results that have appeared in the latest literature may be due to the nature of the subject's clothing and bed-clothes. Not only must measurements of insensible perspiration be made within short periods, but the hygroscopic material included in the weighings should, theoretically at least, be reduced to a minimum, and the conditions of weighing must be such as to avoid variations in the moisture content of the clothing, so far as possible.

Another important consideration, which appears to have been overlooked in at least one investigation, is that the insensible perspiration is, within limits, affected to the same extent as the metabolism by factors that alter the latter. For measurements of the basal insensible perspiration, basal conditions must be observed as rigorously as for determinations of basal metabolism. If the effect of any activity superimposed on the basal state is to be studied, care must be exercised to ensure that no other factors are allowed to operate which also might affect the metabolism. Neglect of this precaution is, no doubt, responsible for the unexpectedly great difference that Heller and Natanson[9] have recorded between the rates of insensible perspiration in the recumbent and the upright positions. Another unexpected result is that reported by Jores.[10] Under conditions of work, fever and certain diseases he found an absolute parallelism between the changes in basal metabolism and the insensible perspiration, but during sleep at night he noted that the insensible perspiration was greater than during rest in the daytime, this despite the well known depressing effect of sleep on the metabolism.[4] Jores also claimed that sometimes long periods must elapse after

8. Heller, H.: Eine Fehlerquelle bei der Bestimmung der Perspiratio insensibilis mit der Sauterwage, Ztschr. f. d. ges. exper. Med. **73**:481, 1930.

9. Heller, H., and Natanson, H.: Der Einfluss der aufrechten Körperhaltung auf die extrarenale Wasserausscheidung, Ztschr. f. d. ges. exper. Med. **65**: 733, 1929.

10. Jores, A.: Perspiratio insensibilis, Ztschr. f. d. ges. exper. Med. **71**:170, 1930.

the assumption of basal conditions before a steady rate of insensible perspiration is established.

Since the experimental results just referred to are at variance with the findings by other investigators on insensible perspiration or are such that they might seriously alter the interpretation of measurements of the insensible perspiration, additional information has been sought experimentally by the Nutrition Laboratory on the following questions:

1. The period that must elapse after the assumption of basal conditions before the rate of loss in body weight by insensible perspiration becomes steady.

2. The effect on this rate of changing from the recumbent to the sitting position.

3. The effect of sleep on this rate (*a*) during the daytime and (*b*) at night.

4. The effect produced on the rate by hindering the loss of water by evaporation from the surfaces of the hands and feet.[11]

THE PERIOD NECESSARY UNDER BASAL CONDITIONS TO ESTABLISH A STEADY RATE OF INSENSIBLE PERSPIRATION

The total duration of the measurements reported by Jores[10] was always at least two hours. According to him, the rate of insensible loss in weight was faster at the beginning of the measurements, even with subjects accustomed to the procedure, and sometimes the rate first became constant only after one and one-half hours. In the experiments to be discussed in the following pages, the subject (a man) arrived at the laboratory in the morning in the postabsorptive state and was allowed to rest quietly for about one-half hour before measurements were taken. He wore his usual street clothing in all experiments. During the observations he lay on a steel mattress suspended from the beam of a 100 Kg. Sauter balance. The mattress was covered with a rubberized sheet and provided with two rubber air pillows. If the statement of the subject or the temperature of the room indicated that the subject was not likely to be comfortably warm during the experiment, he was allowed to lie on a blanket and was covered with another. The subject was weighed by almost counterpoising him by weights (pig-lead or shot) totaling slightly less than his own weight. The beam of the balance was then caused to swing and the time noted at which the swings to each side of the midpoint of the scale were equal. A weight of 10 Gm.

11. An interesting point has been reemphasized by the experiments of Kuno and Ikeuchi (J. Orient. Med. **7**:106, 1927; ibid. **8**:40, 1928) who found that the rate of insensible perspiration from the palms of the hands and the soles of the feet is many times more rapid than that from equal areas of other parts of the body surface.

was then placed on the subject's side of the balance and the time noted when the swings again occurred to equal distances from the midpoint. Since the period of swing of the balance was twenty seconds, the time for the instant of equality of the weight of the counterpoise and that of the subject was recorded only to the nearest half minute, that is, with a possible error of ± fifteen seconds.

In table 1 the rates of insensible perspiration, expressed in grams per hour, are shown for thirteen different experiments. The rates in each experiment have been calculated from the successive periods required for the loss of the first, second and third 10 Gm. of body weight. The total duration of each group of observations was approximately one hour. There is a tendency for the rate of insensible perspiration observed

TABLE 1.—*Rates of Insensible Perspiration During Successive Periods Required to Lose the First, Second and Third 10 Grams of Body Weight (Subject Lying, Postabsorptive)*

Experiment	Insensible Perspiration, Gm. per Hour		
	Period I	Period II	Period III
1	30.8	26.3	29.2
2	31.6	26.1	29.2
3	29.2	26.6	27.0
4	32.0	28.5	27.9
5	30.8	30.0	26.6
6	36.3	32.8	33.3
7	31.6	26.1	25.0
8	25.0	24.0	26.1
9	26.1	29.2	30.0
10	30.8	30.8	33.3
11*	32.4	27.9	27.2
12*	50.0	46.1	41.4
13*	37.5	33.3	30.0
Average†	30.4	28.0	28.8

* Raining when subject came to laboratory.
† Not including experiments 11, 12 and 13.

during the period of the loss of the first 10 Gm., that is, during approximately the first twenty minutes of the experiment,[12] to be slightly higher than during the periods of loss of the second and third 10 Gm. of body weight. There is no such constant difference between the rates during the second and third periods, for in seven of the thirteen experiments the loss during the third period is greater than that during the second period.

On the occasion of experiments 11, 12 and 13 the subject had been exposed to rain on his way to the laboratory. Subsequent examination showed that the ends of his trousers had become damp. The continued

12. Since a certain amount of time was required after the subject lay down to counterpoise him on the balance, the period of measurement of the first 10 Gm. of insensible loss corresponded more nearly to thirty or forty minutes after the lying position was assumed, i.e., the time commonly considered prerequisite for the establishment of basal conditions in basal metabolism measurements.

fall in the rate of insensible perspiration in experiments 12 and 13 (not shown in experiment 11) is therefore probably due to the vaporization of water from the damp clothing. It is well known that woolen clothing can take up considerable amounts of water without becoming obviously wet. Any possibility of the action of this factor should be excluded when determinations are to be made of the insensible perspiration. A desirable modification of the routine of such experiments would be to have subjects who come to the laboratory from outside change at least their outer clothing for clothing that has been kept in the laboratory long enough to have reached equilibrium with the existing conditions of humidity.

The average rates of insensible perspiration for the first ten experiments reported in table 1, that is, not including experiments 11, 12 and 13 that were made on rainy days, are 30.4, 28 and 28.8 Gm. per hour in the first, second and third periods, respectively. Since there is so little difference between the average rate in the first period and the average rates in the second and third periods, one can consider that the rate of loss is constant almost from the start of the experiment. Certainly these averages and the individual values give no evidence of a continued significant fall in the rate of insensible perspiration after the subject has been lying for thirty minutes (including about fifteen minutes for the adjusting and the counterpoising of the subject on the balance, when the insensible loss is not measured). The conclusion is therefore justified that after the assumption of basal conditions the rate of insensible perspiration becomes constant, for all practical purposes, within thirty minutes. This conclusion is in full conformity with all previous findings by the Nutrition Laboratory, which have demonstrated that under basal conditions when the insensible loss in body weight is plotted with reference to the time, a straight line relationship is invariably noted.

The relative humidity in these experiments varied from 21 to 62 per cent, but, as has been noted in earlier observation in this laboratory, there appeared to be no consistent influence of humidity on the rate of insensible loss.

In two experiments measurements of the basal metabolism were made with the student respiration apparatus [13] concurrently with the determinations of the insensible perspiration. In one experiment the insensible perspiration in three consecutive periods was 30, 27.7 and 28.2 Gm. or, on the average, 28.6 Gm. per hour. According to the table published by Benedict and Root [7] showing the twenty-four hour heat

13. Benedict, F. G., and Benedict, C. G.: A Student Form of Respiration Apparatus, Boston M. & S. J. **188**:567, 1923; Ein einfacher Respirationsapparat, Skandinav. Arch. f. Physiol. **44**:87, 1923.

production of man predicted from the insensible perspiration per hour, the predicted metabolism when the insensible loss amounts to 28.6 Gm. would be 1,381 calories. Three actual metabolism measurements made simultaneously with the observations on insensible perspiration showed values of 1,480, 1,431 and 1,452 calories per twenty-four hours, that is, about 7 per cent higher than the predicted metabolism. In the second experiment the insensible perspiration in five consecutive periods was 30, 32.5, 32, 32 and 35.5 Gm., respectively, averaging 32.4 Gm. per hour. The heat production predicted from this average loss would be 1,494 calories per twenty-four hours. Actual measurements of the metabolism gave values of 1,549 calories in each of the first four periods and 1,570 calories in the fifth period, values again but about 7 per cent above the metabolism predicted from the insensible perspiration.

EFFECT OF BODY POSITION ON INSENSIBLE PERSPIRATION

A change in body position is accompanied by a change in metabolism, a somewhat higher metabolism being found in a quiet person when sitting than when lying and a still higher metabolism when standing. The effect of changes in position on the insensible perspiration has been recently studied by Heller and Natanson.[9] The losses of weight during periods of four hours each were observed by means of a balance having a sensitivity of 10 Gm. Owing to the long periods of measurement it was not practicable to maintain the conditions of bodily rest that are required for determinations of basal metabolism. All the subjects were in the fasting state, but some of them received up to 1,000 cc. of water or of a salt solution during the course of the experiment. Those who were in bed were allowed to make slight movements and to converse, but not continually. Those who were in the upright position were allowed to walk quietly about the hospital ward in which the experiments were made, or to sit down, but were not permitted to move about actively, to run, or to assist in carrying things. The result of these vaguely regulated conditions of activity was that the group in bed showed an insensible perspiration from 31 to 46 per cent above the figures predicted [14] from the table of Benedict and Root,[7] and the upright group showed an increase of from 66 to 83 per cent above those figures. The average figure for the subjects in the upright position exceeded that for the subjects in bed by 36 per cent. Thus seemingly a great influence of change in body position was noted by Heller and Natanson. But the unknown effect of the muscular activity in their experiments renders them wholly unsuitable for showing the influence of

14. Indirectly derived, after computation of the basal metabolism from the Harris-Benedict prediction tables.

the alteration of position alone on the rate of loss of weight by insensible perspiration.

With our subject, some direct, short period measurements were made on the effect of change in position from lying to sitting. The rate of insensible perspiration of the subject while lying was first determined in several short successive periods. The subject was then allowed to rise from the bed in which he had been weighed and to sit quietly in a chair, while the bed was replaced by a chair suspended from the beam of the balance. The subject then moved to the suspended chair, was counterpoised, and the measurements of the rate of insensible perspiration were continued. During the intervals between the actual weighings the feet of the subject were supported, and he was in general made as comfortable and relaxed as possible. After a steady rate of insensible perspiration in the sitting position had been established, the subject left the suspended chair and sat quietly, while the chair was replaced by the

TABLE 2.—*Effect of Body Position on Insensible Perspiration (Average Values)*

	Insensible Perspiration, Gm. per Hour		
Experiment	Lying	Sitting	Lying
1	29.2	35.5	26.4
2	31.1	32.7	30.5
3	37.5	37.2	25.9
4	29.0	35.9	26.1
Average	31.7	35.3	27.2

bed. He then lay on the bed, and his rate of insensible perspiration was again determined during several short periods in the recumbent position. All the changes of position were made by the subject deliberately and with as little unnecessary exertion as possible. After each change in position sufficient time was allowed to elapse before observing the insensible loss, so that the effect of the muscular effort involved in the actual change in position would not be included in the measurement.

The results of four different experiments to study the effect of body position are recorded in table 2. Each value represents the average of several continuous observations. Change from the lying to the sitting position caused an increase in the insensible perspiration. The individual results varied greatly, however, in spite of the precautions taken. In the third experiment a slight decrease was observed. In this instance the insensible loss in the lying position was exceptionally high, although it remained constant during the period of measurement. Change from the sitting back to the lying position caused a decrease. The individual decreases again showed considerable variation. The insensible perspiration in the four sitting periods is on the average 5.8 Gm. or 20 per cent higher than the average insensible loss in the eight lying periods. This

increase is remarkably large when compared with the average increase of only 4 per cent which Benedict and Benedict [15] found in the metabolism of a person as a result of a change in position from lying to sitting. Their results likewise showed considerable variation, although the greatest increase observed in the metabolism due to sitting was but 10.8 per cent. It was evident that in the measurements reported in table 2 the subject was not made as comfortable as he could have been when sitting in the chair not suspended from the balance. The somewhat constrained position which could not be completely avoided during the periods of actual weighing may likewise have had a greater effect on the metabolism than was anticipated.

INSENSIBLE PERSPIRATION DURING SLEEP

Three experiments were made on the effect of sleep on the insensible perspiration when the sleep occurred during the daytime and one experiment when the sleep occurred at night. In the three experiments during the daytime the periods of sleep considered ranged from twenty-seven to forty-three minutes. The insensible perspiration during these periods is compared in table 3 with the corresponding values for periods of wakefulness immediately before or after the periods of sleep. There was no discontinuity of observations during the period of transition from sleep to wakefulness or vice versa. The average insensible perspiration during the periods of wakefulness and sleep was 30.2 and 29.6 Gm. per hour, respectively. No significance can be attached to such a small difference between the two values, and the conclusion is that sleep for short periods during the daytime has no appreciable effect on the rate of insensible perspiration.

TABLE 3.—*Effect of Sleep in the Daytime on the Insensible Perspiration*

	Awake		Asleep	
Experiment	Total Time, Min.	Insensible Loss per Hour, Gm.	Total Time, Min.	Insensible Loss per Hour, Gm.
1	33	27.3	43	27.3
2	27	32.8	27	32.8
3	40	30.5	32	28.6
Average		30.2		29.6

In the night experiment, recorded in table 4, sixty-three consecutive minutes of wakefulness were followed by seventy-four consecutive minutes of sleep. The length of each separate period was determined

15. Benedict, F. G., and Benedict, C. G.: Influence sur le métabolisme de la position du corps et des moindres mouvements musculaires, Bull. Soc. scient. d'hyg. aliment. **12**:480, 1924; Body Posture and Minor Muscular Movements as Affecting Heat Production, Proc. Nat. Acad. Sc. **10**:498, 1924.

by the time required for the loss of 10 Gm. in body weight. The observations in this experiment were, unfortunately, not made on the subject in the basal state but were begun about an hour and a half after the ingestion of a light supper consisting of two rolls and butter and a cup of weak tea containing a little milk and sugar. The rate of insensible perspiration changed sharply to a lower level when the subject fell asleep. That this effect is not to be attributed to a gradual fall in insensible perspiration due to the passing off of an initial effect of the food ingested is demonstrated by the values given for the individual periods of the experiment in table 4. These values show clearly that the rate of insensible perspiration varied so slightly during the awake periods that it may be regarded as having been essentially constant. The same is true of the sleep periods. The average insensible perspiration during the awake periods is 28.6 Gm. and that during the sleep

TABLE 4.—*Effect of Sleep at Night on the Insensible Perspiration*

Condition and Time	Length of Period, Min.	Insensible Loss per Hour, Gm.
Awake		
7:41 p. m.	....	....
8:02 p. m.	21.0	28.6
8:24 p. m.	21.5	27.9
8:44 p. m.	20.5	29.3
Average		28.6
Asleep		
9:09 p. m.	25.0	24.0
9:35 p. m.	23.5	23.5
9:58 p. m.	23.5	25.5
10:23 p. m.	25.0	24.0
Average		24.3

periods is 24.3 Gm. per hour. The sleep at night therefore caused an average fall in the rate of insensible perspiration amounting to 15 per cent of the average value for the periods when the subject was awake.

The difference between the effects of sleep in the daytime and at night on the rate of insensible perspiration cannot be ascribed to the difference between the lengths of the periods of sleep under the two conditions. The material change in the rate of insensible perspiration during sleep at night showed itself immediately when the subject fell asleep. The periods of sleep observed in the daytime were long enough to show any similar effect, had it been present. The depth of sleep was not determined in either condition. These results differ fundamentally from those recorded by Jores.[10] He found a large increase in the rate of insensible perspiration during sleep at night. This increase was greatest during the earlier portion of the sleep period. The present results are in harmony with the parallel variation that has been shown to hold between metabolism and insensible perspiration, and with the fact that sleep lowers the basal metabolism about 10 per cent.[4]

INSENSIBLE PERSPIRATION FROM HANDS AND FEET

Experiments were made to determine the effect of hindering the insensible loss of water from the hands and feet. In one series of observations the insensible loss from the hands and feet was hindered without otherwise modifying the procedure that has already been described for the determination of the insensible perspiration. In another series the loss from hands and feet was not only obstructed but the feet were warmed at the same time, and in still a third series the loss was hindered from the hands only. The loss of water from the feet was hindered, if not prevented, by covering the feet with rubber overshoes chosen to fit the subject's feet as closely as possible. The upper border of the overshoes was fastened to the skin by a strip of adhesive plaster. The hands were covered with rubber gloves and tightly fitting rubber bands were placed around the wrists over the gloves. The measurements secured when both the hands and feet were covered in this way are given in table 5. In three of the experiments

TABLE 5.—*Effect on Insensible Perspiration of Covering the Hands and Feet to Hinder Their Loss of Water*

Experiment	Insensible Perspiration, Gm. per Hour			
	Uncovered	Covered	Uncovered	Covered
1	28.5	20.6	25.2	....
2	....	28.4	33.6	28.6
3	31.6	25.5	31.0	....
4	25.3	20.3	24.3	....
5	....	20.4	25.7	....

the insensible perspiration was determined in the ordinary way before the hands and feet were covered. In the other two experiments the hands and feet were covered first. The relative humidity varied from 35 to 56 per cent and the room temperature from 16.1 to 25.9 C. In every experiment the rate of insensible perspiration was markedly diminished by hindering the loss from the hands and feet. When the covering was removed after a period long enough to allow equilibrium in the loss to become established again under the altered conditions, the rate of insensible perspiration soon returned to approximately its original value. In these experiments the mean value of the insensible perspiration for all instances when the hands and feet were uncovered was 28.3 Gm. per hour. When they were covered, the average rate fell to 24 Gm. The difference is 4.3 Gm. The insensible loss from the hands and feet therefore amounts, on the average, to 15 per cent of the total insensible perspiration under basal conditions.

It has been shown by Benedict and Benedict [2] that under basal conditions the loss of water from the skin is approximately 50 per cent of the total insensible perspiration. Since the total insensible loss of

our subject in the experiments reported in table 5 averaged 28.3 Gm. per hour, the calculated total loss from the skin would be about 14.2 Gm. By hindering the loss of water from the hands and feet the loss from the skin was decreased by 4.3 Gm. Hence the loss from hands and feet represents 30 per cent of the total skin loss. Du Bois and Du Bois [16] showed that the area of the hands and feet, measured to the wrists and ankles, respectively, amounts to approximately 12 per cent of the total area of the body. The hands and feet must therefore lose water under the conditions of temperature and humidity in our experiments nearly three times as fast per unit of skin area as the rest of the surface of the body per equal unit of skin area.

In two experiments the feet of the subject were heated by applying to the bare soles a rubber water bottle containing water at a temperature as hot as he could endure. Observations under these conditions were made with and without the rubber coverings on the hands and feet. The relative humidity was 55 per cent and the room temperature 20 C. In the first experiment the insensible loss when the extremities were uncovered averaged 42 Gm., when they were covered 32 Gm., and when they were again uncovered 48.2 Gm. per hour. In the second experiment observations made in the same order gave results of 39.1, 25.9 and 30.9 Gm., respectively. According to the data in table 1 the average insensible perspiration of this subject under ordinary basal conditions was about 28.4 Gm. per hour. Warming the feet (but with the extremities not covered) caused an increase on the average to 40.5 Gm., that is, an increase of 40 per cent. When the hands and feet were covered, there was, as in the previous experiments reported in table 5, a marked decrease in the rate of insensible perspiration from an average of 40.5 Gm. to an average of 29 Gm. In these two experiments, therefore, the average decrease amounted to 12 Gm., in striking contrast to the decrease of 4.3 Gm. noted in the experiments recorded in table 5 in which the feet had not previously been warmed.

In two experiments the effect on the insensible perspiration of covering the hands alone was observed. A diminution of the insensible loss was noted, although to a lesser degree than when both hands and feet were covered.

The experiments reported in the foregoing pages accentuate the importance of observing strictly basal conditions when one is measuring insensible perspiration. The experience of the Nutrition Laboratory, certain hospital usage in Boston, and particularly the experience of Professor Newburgh,[17] emphasize the belief that the accurate measure-

16. Du Bois, D., and Du Bois, E. F.: The Measurement of the Surface Area of Man, Arch. Int. Med. **15**:868 (May) 1915.

17. Newburgh, L. H., and Johnston, M. W.: The Exchange of Energy Between Man and the Environment, Springfield, Ill., Charles C. Thomas, 1930.

ment of the insensible perspiration may have considerable clinical value. The method has its limitations, which must be clearly recognized, and it is obvious that it must not be misused.

SUMMARY

1. When measured under the usual conditions obtaining in basal metabolism experiments, the rate of insensible perspiration of an adult man became constant within thirty minutes after the assumption of the lying position.

2. Changing from the lying to the sitting position caused an increase of 20 per cent in the rate of insensible perspiration under the special experimental conditions.

3. Sleep during the daytime had no significant effect on the rate of insensible perspiration. Sleep at night lowered it markedly.

4. About 15 per cent of the total loss by insensible perspiration was due to the loss from the surfaces of the hands and feet. Of the total skin loss, 30 per cent was derived from the surfaces of the hands and feet.

5. The rate of loss from the hands and feet was approximately three times greater than that from the rest of the skin per equal unit of skin area.

6. Heating the feet increased the loss by insensible perspiration considerably.

CLINICAL SIGNIFICANCE OF VOLUME AND HEMOGLOBIN CONTENT OF THE RED BLOOD CELL

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In 1864, Welcher [1] described the first method for determining the volume of the erythrocyte and measured in cubic microns the volume of the normal cell of man and of many lower animals. By his ingenious, but inaccurate, method, Welcher also showed that in chlorosis the red cells may be smaller than normal, and thus he made the first clinical application of the determination of the volume of the erythrocyte. Hayem,[2] the father of clinical hematology, early recognized the importance of variation in the size of the red cells although he measured only the diameter. Laache,[3] in the first monograph on anemia, measured the diameter of the red cells in every case of anemia, and showed especially the great significance of macrocytosis of the erythrocytes in pernicious anemia. Malassez,[4] one of the important early contributors to hematology, reported the hemoglobin content in micromicrograms per cell in different types of anemia. Using Welcher's figures for the volume of the normal cell, Malassez calculated the hemoglobin also in percentage per unit volume of cell. Similar calculations were made by Hart [5] in 1881.

Hedin's development of the hematocrit [6] afforded the first simple and direct method for determining the volume of the red blood cell. Herz [7] first used the hematocrit to measure the mean individual cell volume, which he designated "das mittlere Volumen der einzelnen Zellen." He calculated also the "specific hemoglobin content of the cell," which is the same as the saturation index. It remained, however, for Capps [8] to demonstrate, in 1903, the clinical significance of varia-

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1. Welcher, H.: Grösse, Zahl, Volum, Oberfläche und Farbe der Blutkörperchen bei Menschen und bei Tieren, Ztschr. f. rat. Med. **20**:257, 1863.

2. Hayem, G.: Recherches sur l'anatomie normale et pathologique du sang, Paris, Masson & Cie, 1878, p. 143.

3. Laache, S.: Die Anämie, Kristiania, Malling, 1883, p. 276.

4. Malassez, L.: Sur la richesse en hémoglobine des globules rouges du sang, Arch. de physiol. norm. et path. **4**:637, 1877.

5. Hart, E.: Micrometric Numeration of the Blood Corpuscles and the Estimation of Their Hemoglobin, Quart. J. Micr. Sc. **21**:132, 1881.

6. Hedin, S. G.: Hämatokriten, en ny apparat för blodundersökning, Skandinav. Arch. f. Physiol. **2**:134, 1890-1891.

7. Herz, Max: Blutkrankheiten, Virchows Arch. f. path. Anat. **133**:339, 1893.

8. Capps, J. A.: A Study of Volume Index: Observations upon the Volume of the Erythrocyte in Various Diseased Conditions, J. M. Research **10**:367, 1903.

tions in the volume of the average erythrocyte, which he recorded in terms of his volume index. Following Capps' important contribution little use was made of cell volume determinations by hematologists for a number of years. In the past ten years, however, interest in this phase of blood studies has been revived, and a number of articles on cell size have appeared.[9]

It is the purpose of this paper to summarize the clinical significance of the accurate determination of the volume and hemoglobin content of the red cell in health and disease and to report the results of such studies on 444 normal and abnormal persons.

METHODS

In determining the relative red cell volume, I have used the hematocrit method. This method has been criticized, especially by Ponder and Saslow,[10] as not giving

9. Alder, Albert: Viscosimetriches Blutkörperchenvolumbestimmung: Studien über Grösse und Haemoglobinfülling der Erythrocyte, Cor.-Bl. f. schweiz. Aerzte **48**:1405, 1918. Bonninger, M.: Die Bedeutung des Blutkörperchenvolumens für die klinische Blutuntersuchung, Ztschr. f. klin. Med. **87**:450, 1919. Csaki, L.: Die Volummessung der rothen Blutkörperchen bei verschiedenen Krankheiten, Ztschr. f. klin. Med. **93**:405, 1922. Froelich, Carrie: Ueber genaue Bestimmung des Färbeindex der roten Blutkörperchen, Färbeindex (Zahl) und Färbeindex (Volumen), Folia haemat. **27**:109, 1921-1922. Haden, R. L.: Accurate Criteria for Differentiating Anemias, Arch. Int. Med. **31**:766 (May) 1923. Rossdale, George: Observations with the Haematocrit, Volume-Colour Index, Quart. J. Med. **16**:245, 1923. Haden, R. L.: The Value of Volume Index in the Diagnosis of Pernicious Anemia, J. A. M. A. **83**:671 (Aug. 30) 1924; The Volume and Hemoglobin Content of the Erythrocyte in Health and Disease, Folia haemat. **31**:113, 1925. von Boros, J.: Ueber Grösse, Volumen und Form der menschlichen Erythrozyten und deren Zusammenhang, Wien. Arch. f. inn. Med. **12**:243, 1926. Osgood, E. E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standards, Arch. Int. Med. **37**:685 (May) 1926. Osgood, E. E., and Haskins, H. D.: Relation Between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women, Arch. Int. Med. **39**:634 (May) 1927. Jörgensen, S., and Warburg, E. J.: The Indices and Diameters of the Erythrocytes and the Best Hematological Criterion of Pernicious Anemia, Acta med. Scandinav. **46**:109, 1927. Wintrobe, M. M., and Miller, M. W.: Normal Blood Determinations in the South, Arch. Int. Med. **43**:96 (Jan.) 1929. Wintrobe, M. M.: Blood of Normal Young Women Residing in a Subtropical Climate, Arch. Int. Med. **45**:287 (Feb.) 1930; The Volume and Hemoglobin Content of the Red Blood Corpuscle, Am. J. M. Sc. **177**:513, 1929. Murphy, W. P., and Fitzhugh, G.: Red Blood Cell Size in Anemia: Its Value in Differential Diagnosis, Arch. Int. Med. **46**:440 (Sept.) 1930. Wintrobe, M. M.: Hemoglobin Content, Volume, and Thickness of the Red Blood Corpuscle in Pernicious Anemia and Sprue, and the Changes Associated with Liver Therapy, Am. J. M. Sc. **181**: 217, 1931. Haden, R. L.: Methods and Clinical Value of the Determination of the Size of the Red Blood Cell, Am. J. M. Sc. **181**:597, 1931.

10. Ponder, E., and Saslow, G.: The Measurement of Red Cell Volume, J. Physiol. **70**:18, 1930.

correct absolute values. It remains, however, the one practical method available, and when properly done gives values that check closely with those of other entirely different methods, such as that devised by Bleibtreu.[11]

In the hematocrit method an anticoagulant that does not change the volume of the cells should be employed. Hirudin and heparin are satisfactory but expensive. I have used an isotonic (1.4 per cent) solution of sodium oxalate,[12] which is decidedly preferable to a solid or a concentrated solution of sodium or potassium oxalate which shrinks the cells. The only advantage of the latter procedure is the use of smaller amounts of blood, yet there is seldom any objection to taking 20 cc. of blood from a patient. The greater the extent of the anemia the smaller the volume of cells removed; so the amount of cells removed is always relatively the same. A normal person has roughly 2,500 cc. of packed cells; hence, in taking 20 cc. of blood, about one two hundred and fiftieth or 0.4 per cent of the total cell volume is removed. Since the blood volume changes little, a person with a cell volume of 40 per cent of normal would have only 4 cc. of packed cells removed, which is still 0.25 per cent of the amount of cells present.

My procedure is as follows: I remove 20 cc. of blood from the median basilic vein, and add exactly 10 cc. to 2 cc. of 1.4 per cent sodium oxalate solution contained in an accurately graduated 12 or 15 cc. centrifuge tube. This is spun in an International no. 2 centrifuge for one hour at 2,500 revolutions per minute. The remaining 10 cc. has 2 drops of a saturated solution of potassium oxalate added to it and is used for the cell count and hemoglobin determination. All cell counts have been made with counting chambers and pipets certified as correct by the United States Bureau of Standards. Nearly all the hemoglobin estimations have been done by the oxygen capacity method using the Van Slyke apparatus. Recently hemoglobin readings have been made with the Haden-Hausser hemoglobinometer [13] which has given readings that check closely with the gasometric procedure. The determinations that were made by means of the hemoglobinometer are indicated in the tables by a star. The number of determinations made by this method is only 31 among a total of over 500 determinations reported here.

In calculating the percentage of hemoglobin, 15.4 Gm. per hundred cubic centimeters is taken as 100 per cent since this is the average amount that I have found per hundred cubic centimeters per five million cells in 100 normal men and women. The amount of packed cells will vary somewhat, although very little, with the time and force of centrifugation. With one centrifugation for one-half hour, 48 cc. of packed cells per hundred cubic centimeters per five million cells was obtained; with another for one hour, 45 cc. With the centrifuge used most of the time and employing one hour's centrifugation 46 cc. was obtained, so all the results have been corrected to this figure, which is taken as 100 per cent.

The size of the cell may be measured by determining the diameter. Since the volume varies as the cube of the diameter, it is apparent that the volume is a much more sensitive indicator of variation in size than is the diameter. This point is illustrated in figure 1.

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11. Bleibtreu, M., and Bleibtreu, L.: Eine Methode zur Bestimmung des Volums der körperliche Elemente in Blut, Arch. f. d. ges. Physiol. **51**:151, 1891-1892.

12. Haden, R. L.: The Technique of Determination of the Relative Mass, the Individual Cell Volume and the Volume Index of the Erythrocytes of Man, J. Lab. & Clin. Med. **15**:736, 1930.

13. Haden, R. L.: A New Hemoglobinometer, J. Lab. & Clin. Med. **16**:68, 1930.

TERMINOLOGY

Number.—The number index is the number of erythrocytes relative to normal (5,000,000 equals 100 per cent).

Volume.—The volume coefficient [14] is the number of cubic centimeters of packed cells per five million cells per hundred cubic centimeters of blood. This is calculated by dividing the number of cubic centimeters of packed cells per hundred cubic centimeters by the number index. The normal volume coefficient in this series was 46.

The mean corpuscular volume [15] is the mean volume of a single red blood cell in cubic microns. This is calculated by dividing the volume of packed cells in a unit volume of blood by the number of cells contained therein. The normal in this series was 92 cubic microns.

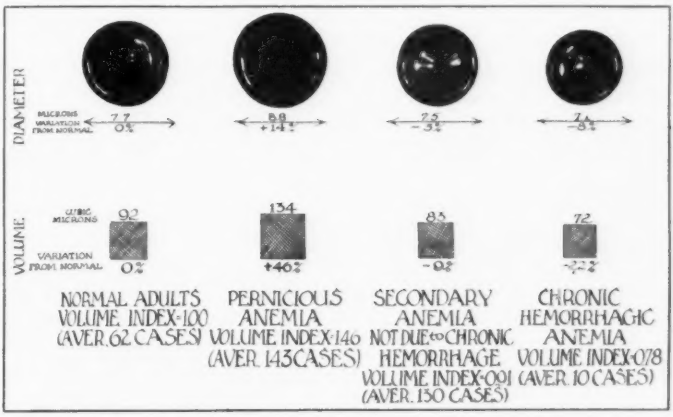

Fig. 1.—Relation of cell volume to cell diameter. The mean corpuscular volume is the most sensitive indicator of variation in cell size.

The volume index is the mean volume of a single red cell relative to normal. This is calculated by dividing the volume of packed cells in per cent of normal by the number of cells in per cent of normal, or the number index, or by dividing the observed mean corpuscular volume by the normal mean corpuscular volume. The normal limits of the volume index are taken as 0.90 and 1.10.

Hemoglobin Content.—The hemoglobin coefficient [14] is the number of grams of hemoglobin per five million cells per hundred cubic centimeters of blood. This is calculated by dividing the observed number of grams of hemoglobin per hundred cubic centimeters by the number index. The normal hemoglobin coefficient in this series was 15.4 Gm.

14. Term suggested by Osgood.
15. Term suggested by Wintrobe.

The mean corpuscular hemoglobin [15] is the mean hemoglobin content of a single red cell in micromicrograms. This is calculated by dividing the number of micrograms of hemoglobin in a unit volume of blood by the number of cells contained therein. The normal mean corpuscular hemoglobin content in my series was 30.8 micromicrograms.

The color index is the mean hemoglobin content of a single cell relative to normal. This is calculated by dividing the hemoglobin in per cent of normal by the number of cells in per cent of normal or the number index, or by dividing the observed mean corpuscular hemoglobin by the normal mean corpuscular hemoglobin. The normal limits of the color index are taken as 0.90 and 1.10.

Hemoglobin Concentration.—The mean corpuscular hemoglobin concentration [15] is the mean hemoglobin concentration in per cent per unit volume of cells. This is calculated by dividing the hemoglobin in a unit volume of blood by the volume of packed cells contained therein. The normal corpuscular hemoglobin concentration in this series was 33.7 per cent.

The saturation index is the mean corpuscular hemoglobin concentration relative to normal. This is calculated by dividing the hemoglobin in per cent of normal by the number of packed red cells in per cent of normal, or by dividing the color index by the volume index. The normal limits of the color index are taken as 0.90 and 1.10.

The absolute volumes for the red cell constants seemingly vary geographically.[16] For this reason it seems preferable in clinical work to express the volume, hemoglobin content and hemoglobin concentration in per cent of normal (volume, color and saturation index) rather than in cubic microns, micromicrograms and per cent. With correct adjustment the indexes are everywhere always within normal limits (0.90 and 1.10), even with a great difference in the volume of the average cell in cubic microns and in the hemoglobin content in micromicrograms.

NORMAL OBSERVATIONS

The uniformity of the volume and hemoglobin content of the red cell in healthy persons in a given location is most remarkable. There is little variation in cell size in different persons, and single cells vary only within very narrow limits. In determining my standards, I have studied 100 normal men and women by the methods described. The typical determinations in 10 persons and a summary for the entire group are shown in table 1. The cell volume, hemoglobin content and hemoglobin concentration did not vary from the mean more than ± 10 per cent and in few persons more than ± 5 per cent. The volume

16. Haden, R. L.: The Geographic Variation in the Size of the Red Cells, J. Lab. & Clin. Med. **14**:1120, 1929.

TABLE 1.—*Determinations in One Hundred Normal Men and Women*

Sex	Red Blood Cells per Cu. Mm., Millions	Packed Red Cells: Hematocrit Reading per 100 Cc., in Cc.	Packed Red Cells: Per Cent of Normal	Packed Red Cells: Volume Coefficient, Cc.	Mean Corpuscular Volume, Cubic Microns	Volume Index	Hemoglobin: Gm. per 100 Cc.	Hemoglobin: Per Cent of Normal	Hemoglobin: Hemoglobin Coefficient, Gm.	Mean Corpuscular Hemoglobin, Micromicrograms	Color Index	Mean Corpuscular Hemoglobin Concentration, per Cent	Saturation Index
						Typical Determinations							
M	4.96	44	90	45	90	0.98	15.06	98	15.4	30.8	1.00	34.2	1.02
M	4.73	43	91	44	88	0.96	14.95	97	15.8	31.6	1.03	35.9	1.07
M	4.52	44	96	48	96	1.04	14.02	91	15.5	31.0	1.01	32.7	0.97
M	4.59	47	100	46	92	1.01	15.42	100	15.2	30.4	0.99	33.1	0.98
M	5.06	46	100	46	92	1.00	15.52	101	15.4	30.8	1.00	33.7	1.00
M	5.02	40	100	47	94	1.02	16.50	107	15.9	31.8	1.03	33.9	1.01
M	5.18	40	106	47	94	1.00	13.15	85	16.2	32.6	1.06	35.7	1.06
F	4.03	38	83	47	92	1.00	12.70	83	14.6	29.2	0.95	32.1	0.95
F	4.35	40	87	46	90	0.98	13.26	86	14.4	28.8	0.94	32.4	0.96
F	4.62	41	89	45	90	0.98	14.25	93	15.2	30.4	0.99	34.0	1.01
F	4.74	45	94	45	90								
							Summary						
	4.78	42.7	95	46	92	1.00	14.75	95	15.43	30.8	1.00	33.7	1.00

coefficient was 46, the hemoglobin coefficient 15.4 Gm. and the hemoglobin concentration 33.7 per cent. The average volume, color and saturation indexes were 1.00. These figures were taken as 100 per cent in calculating the percentages and indexes. The normal observations in 100 men and women are shown graphically in figure 2.

LABORATORY CLASSIFICATION OF ANEMIA ON THE BASIS OF VOLUME AND HEMOGLOBIN CONTENT

The laboratory classification of anemia has always been unsatisfactory. A rough differentiation into primary and secondary types is frequently used. The anemias showing a color index greater than 1.00

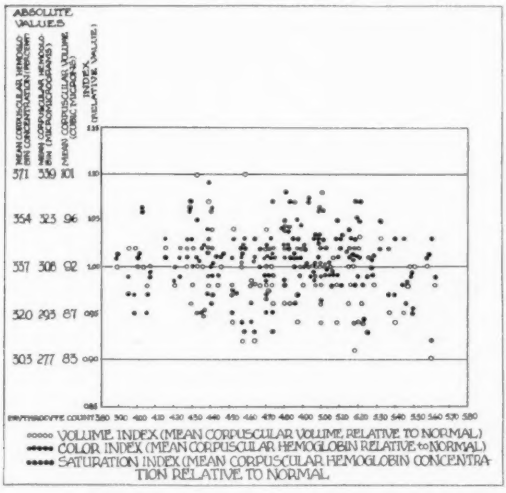
ABSOLUTE VALUES
371 339 101
354 323 96
337 308 92
320 293 87
303 277 85
ERYTHROCYTE COUNT
VOLUME INDEX (MEAN CORPUSCULAR VOLUME, RELATIVE TO NORMAL)
COLOR INDEX (MEAN CORPUSCULAR HEMOGLOBIN RELATIVE TO NORMAL)
SATURATION INDEX (MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION RELATIVE TO NORMAL

Fig. 2.—The indexes and erythrocyte constants in 100 normal men and women. Note the very slight variation for the entire group.

are usually classified as primary and those showing a color index of 1.00 or less as secondary. Hampson and Shackle [17] have suggested the classification of anemias on the basis of cell size, using the terms megalocytic and nonmegalocytic. Wintrobe [18] suggested four groups: (1) macrocytic, (2) normocytic, (3) simple microcytic and (4) hypochromic. Certainly the most logical laboratory classification is based

17. Hampson, A. C., and Shackle, J. W.: Megalocytic and Nonmegalocytic Anemia, Guy's Hosp. Rep. **74**:193, 1924.

18. Wintrobe, M. M.: Classification of the Anemias on the Basis of Differences in Size and Hemoglobin Content of the Red Corpuscles, Proc. Soc. Exper. Biol. & Med. **27**:1071, 1930.

on all three variables of the erythrocyte, namely, number, size and hemoglobin content. The following terms may well be employed to indicate variations that have been observed in these factors.

Number	Hypercythemic: red cell count > normal Normocythemic: red cell count within normal limits Hypocythemic: red cell count < normal
Volume	Macrocytic: mean corpuscular volume > normal (VI > 1.10) Normocytic: mean corpuscular volume, normal (VI = 0.90-1.10) Microcytic: mean corpuscular volume < normal (VI < 0.90)
Hemoglobin content	Hyperchromic: mean corpuscular hemoglobin > normal (CI > 1.10) Normochromic: mean corpuscular hemoglobin, normal (CI = 0.90-1.10) Hypochromic: mean corpuscular hemoglobin < normal (CI < 0.90)

All the different types of anemia that may occur from this standpoint are:

Normocythemic	Normocytic and hypochromic Microcytic and hypochromic
Hypercythemia	Normocytic and hypochromic Microcytic and hypochromic
Hypocythemic	Macrocytic and hyperchromic Macrocytic and normochromic Macrocytic and hypochromic Normocytic and normochromic Normocytic and hypochromic Microcytic and hypochromic

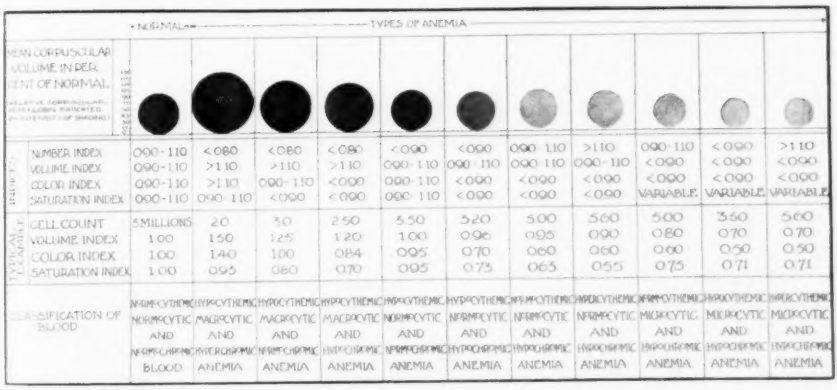
NORMAL
TYPES OF ANEMIA
MEAN CORPUSCULAR VOLUME IN PERCENT OF NORMAL
INDICES
NUMBER INDEX 090-110 <080 <080 <080 <090 <090 090-110 >110 090-110 <090 >110
VOLUME INDEX 090-110 >110 >110 >110 090-110 090-110 090-110 090-110 <090 <090 <090
COLOR INDEX 090-110 >110 090-110 <090 090-110 <090 <090 <090 <090 <090 <090
SATURATION INDEX 090-110 090-110 <090 <090 090-110 <090 <090 <090 VARIABLE VARIABLE VARIABLE
TYPICAL CASE
CELL COUNT 5 MILLIONS 2.0 3.0 2.50 3.50 3.20 3.00 3.60 3.00 3.50 3.60
VOLUME INDEX 1.00 1.50 1.25 1.20 1.00 0.96 0.95 0.90 0.80 0.70 0.70
COLOR INDEX 1.00 1.40 1.00 0.84 0.95 0.70 0.60 0.60 0.60 0.50 0.50
SATURATION INDEX 1.00 0.93 0.80 0.70 0.95 0.73 0.65 0.55 0.75 0.71 0.71
CLASSIFICATION OF BLOOD
NORMOCYTHEMIC NORMOCYTIC AND NORMOCHROMIC BLOOD
HYPERCYTHEMIC MACROCYTIC AND HYPERCHROMIC ANEMIA
HYPERCYTHEMIC MACROCYTIC AND NORMOCHROMIC ANEMIA
HYPERCYTHEMIC MACROCYTIC AND HYPOCHROMIC ANEMIA
HYPOCYTHEMIC NORMOCYTIC AND NORMOCHROMIC ANEMIA
HYPOCYTHEMIC NORMOCYTIC AND HYPOCHROMIC ANEMIA
NORMOCYTHEMIC HYPOCYTIC AND NORMOCHROMIC ANEMIA
HYPOCYTHEMIC MICROCYTIC AND NORMOCHROMIC ANEMIA
NORMOCYTHEMIC MICROCYTIC AND HYPOCHROMIC ANEMIA
HYPOCYTHEMIC MICROCYTIC AND HYPOCHROMIC ANEMIA
HYPOCYTHEMIC MICROCYTIC AND HYPOCHROMIC ANEMIA

Fig. 3.—The different types of anemia classified on the basis of number, volume and hemoglobin content of the erythrocytes.

These different types of anemia are illustrated in figure 3. The circles indicate relative volume, not diameter, and the intensity of color indicates the relative hemoglobin content. A typical example of each type of anemia is given. Every anemia should be thought of in terms of number, volume and hemoglobin content of the average erythrocyte, and every case should be classified on such criteria. An anemia with a red cell count of 3.50 millions, a volume index of 0.75 and a color index of 0.65 is reported as a hypocythemic, microcytic and hypochromic anemia rather than simply as "secondary" anemia. Likewise

an anemia with a count of 2.00 millions and a volume and color index of 1.50 is recorded as hypocythemic, macrocytic and hyperchromic rather than "primary."

OBSERVATIONS IN DIFFERENT CLINICAL GROUPS OF ANEMIA

The clinical classification of anemia is even more confusing than the laboratory classification. Every anemia, however, is due to increased blood loss or decreased blood formation or to a combination of these two factors. Increased blood loss may be mechanical or may result from increased destruction within the body, and the anemias due to decreased blood formation may result from a qualitative depression of bone marrow activity or may be the result of quantitative defect due to an actual decrease in bone marrow tissue. The clinical classification of anemia that I have used with the more common causes in each group is as follows:

I. Increased blood loss (acute or chronic)
  A. Mechanical loss
    1. Uterine bleeding
    2. Hemorrhoids
    3. Peptic ulcer
    4. Disturbances of blood coagulation
    5. Trauma
  B. Accelerated destruction
    1. Chronic hemolytic jaundice
    2. Acute hemolytic anemia
    3. Splenic anemia

II. Decreased blood formation
  A. Qualitative defect
    1. Malignant growth
    2. Infection
    3. Chronic intoxication
    4. Metabolic disturbance
    5. Dietary deficiency
    6. Achlorhydria (simple)
    7. Pernicious anemia
  B. Quantitative defect
    1. A decrease in the bone marrow by bone disease, malignant or leukemic infiltration

I have grouped all the anemias studied according to this clinical classification. In the tables typical examples of the different types are given to show the extremes of the determinations. In table 2 are shown the anemias due to acute mechanical blood loss. Here the number of cells is reduced without change in the mean volume, and with little change in the hemoglobin content. A part of the circulating blood is sliced off, so to speak, and the fraction remaining is relatively normal.

TABLE 2.—*Determinations in Anemia Due to Mechanical Blood Loss from Acute Hemorrhage*

Red Blood Cells per Cu. Mm., Millions	Packed Red Cells: Hematocrit Reading per 100 Cc., in Cc.	Packed Red Cells: Per Cent of Normal	Packed Red Cells: Volume Coefficient, Cc.	Mean Corpuscular Volume, Cubic Microns	Volume Index	Hemoglobin: Gm. per 100 Cc.	Hemoglobin: Per Cent of Normal	Hemoglobin: Hemoglobin Coefficient, Gm.	Mean Corpuscular Hemoglobin, Micromicrograms	Color Index	Mean Corpuscular Hemoglobin Concentration, per Cent	Saturation Index	Diagnosis
						Typical Determinations							
0.93	9	20	50	100	1.09	2.31	15	12.3	24.6	0.80	24.1	0.72	Hemophilia
1.08	12	25	51	102	1.10	3.56	23	16.2	32.4	1.05	30.7	0.92	Duodenal ulcer
1.38	12	27	45	90	0.99	3.85	25	14.0	28.0	0.91	30.7	0.92	Essential thrombopenia
1.65	15	33	46	92	1.00	4.63	30	13.8	27.6	0.90	30.1	0.90	Gastric hemorrhage
2.50	24	54	50	100	1.08	7.55	49	15.1	30.2	0.98	30.4	0.91	Hemophilia
2.62	23	50	45	90	0.97	6.78	44	13.1	26.2	0.85	29.4	0.88	Gastric hemorrhage
3.05	29	62	47	94	1.01	8.63	56	14.0	28.0	0.91	30.1	0.90	Hemophilia
3.44	32	69	46	92	1.00	9.87	64	14.3	28.6	0.93	31.1	0.93	Essential thrombopenia
3.76	35	75	46	92	1.00	11.52	75	15.4	30.8	1.00	33.5	1.00	Hemophilia
4.17	37	80	45	90	0.97	11.00	71*	13.1	26.2	0.85	30.0	0.89	Gastric hemorrhage
						Summary							
2.33	22	47	46	92	1.00	6.62	43	14.17	28.3	0.92	30.7	0.92	Average in 14 cases

* Determination made by means of the hemoglobinometer.

TABLE 3.—*Determinations in Anemia Due to Mechanical Blood Loss from Chronic Hemorrhage*

Red Blood Cells per Cu. Mm., Millions	Packed Red Cells: Hematocrit Reading per 100 Cc., in Cc.	Packed Red Cells: Per Cent of Normal	Packed Red Cells: Volume Coefficient, Cc.	Mean Corpuscular Volume, Cubic Microns	Volume Index	Hemoglobin: Gm. per 100 Cc.	Hemoglobin: Per Cent of Normal	Hemoglobin: Hemoglobin Coefficient, Gm.	Mean Corpuscular Hemoglobin, Micromicrograms	Color Index	Mean Corpuscular Hemoglobin Concentration, per Cent	Saturation Index	Diagnosis
						Typical Determinations							
1.53	15	32	48	96	1.05	3.23	21	10.6	21.2	0.69	23.2	0.66	Hemorrhoids
1.98	15	33	39	78	0.85	3.39	22	8.5	16.9	0.55	23.6	0.67	Essential thrombopenia
2.04	19	42	47	94	1.02	4.65	30	11.2	22.4	0.73	24.0	0.71	Menorrhagia
2.41	16	35	33	66	0.73	4.16	27	8.6	17.3	0.56	26.0	0.77	Hemorrhoids
3.00	22	47	36	72	0.78	5.70	37	9.6	19.1	0.62	26.7	0.79	Hemorrhoids
3.07	26	56	41	82	0.90	5.70	37	9.2	18.5	0.60	23.6	0.67	Hemorrhoids
3.24	24	52	37	74	0.80	6.32	41	9.7	19.4	0.63	26.7	0.79	Menorrhagia
3.43	29	63	42	84	0.91	7.85	51	11.4	22.8	0.74	27.4	0.81	Menorrhagia
3.93	31	67	34	68	0.75	8.78	57	11.2	22.4	0.73	28.7	0.85	Gastric ulcer
4.17	25	54	30	60	0.65	6.93	45*	8.2	16.3	0.53	28.4	0.84	Menorrhagia
						Summary							
3.25	25	54	38	76	0.83	6.62	43	10.2	20.4	0.66	27.0	0.80	Average in 34 cases

* Determination made by means of the hemoglobinometer.

In chronic mechanical blood loss the determinations are quite different (table 3). Here with a varying cell count the mean cell volume is practically always decreased and the hemoglobin content decreased even more. The average cell count in this group was 3.25 millions, the volume index 0.83, the color index 0.66 and the saturation index 0.90.

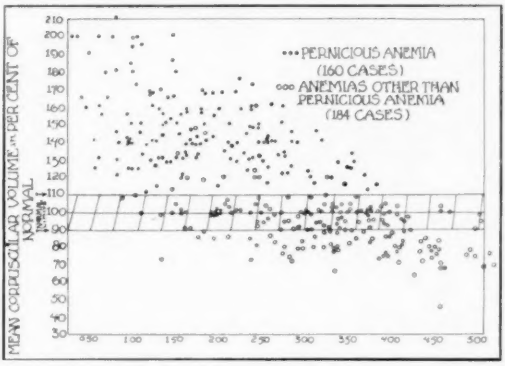
MEAN CORPUSCULAR VOLUME IN PER CENT OF NORMAL
••• PERNICIOUS ANEMIA (160 CASES)
ooo ANEMIAS OTHER THAN PERNICIOUS ANEMIA (184 CASES)

Fig. 4.—The mean corpuscular volume of the erythrocyte in pernicious anemia contrasted with that in other types of anemia. The volume is constantly high in pernicious anemia and seldom above normal in other types.

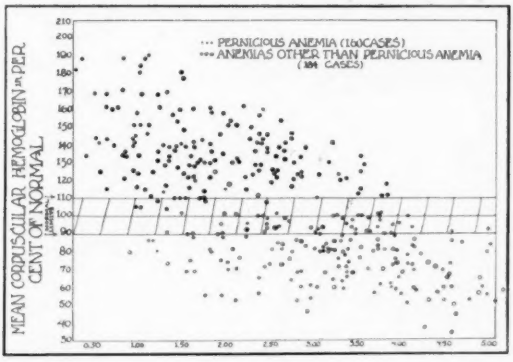
MEAN CORPUSCULAR HEMOGLOBIN IN PER CENT OF NORMAL
••• PERNICIOUS ANEMIA (160 CASES)
ooo ANEMIAS OTHER THAN PERNICIOUS ANEMIA (184 CASES)

Fig. 5.—The mean corpuscular hemoglobin of the erythrocyte in pernicious anemia contrasted with that in other types of anemia.

The anemias due to increased blood destruction constitute an interesting group (table 4). The cell volume is seldom decreased and is often increased. If many reticulocytes are present, the average volume is usually greater than normal since reticulocytes tend to be larger than normal. The average cell count in this group was 2.69, the volume index 1.04, the color index 0.93 and the saturation index 0.93.

TABLE 4.—*Determinations in Anemia Due to Increased Blood Loss from Accelerated Blood Destruction*

Red Blood Cells per Cu.Mm., Millions	Packed Red Cells: Hematocrit Reading per 100 Cc., in Cc.	Packed Red Cells: Per Cent of Normal	Packed Red Cells: Volume Coefficient, Cc.	Mean Corpuscular Volume, Cubic Microns	Volume Index	Hemoglobin: Gm. per 100 Cc.	Hemoglobin: Per Cent of Normal	Hemoglobin: Hemoglobin Coefficient, Gm.	Mean Corpuscular Hemoglobin, Micromicrograms	Color Index	Mean Corpuscular Hemoglobin, Concentration, per Cent	Saturation Index	Diagnosis
						Typical Determinations							
1.50	16	34	52	104	1.14	5.08	33	16.9	33.9	1.10	32.4	0.97	Acute hemolytic anemia (infection)
1.58	19	42	64	128	1.34	6.00	34	16.9	33.9	1.10	27.4	0.82	Splenic anemia
1.83	24	53	66	132	1.43	6.93	45*	19.2	38.5	1.25	27.0	0.81	Chronic hemolytic jaundice
2.05	22	48	54	108	1.17	7.40	48*	18.0	36.0	1.17	33.7	1.00	Chronic hemolytic jaundice
2.34	27	57	56	112	1.21	8.02	52*	17.1	34.2	1.11	30.1	0.90	Phenylhydrazine poisoning
2.43	27	60	55	110	1.20	7.55	49	14.5	29.0	1.00	27.0	0.81	Toxic hepatitis
2.50	21	47	43	86	0.94	7.24	47	14.5	29.0	0.94	33.5	1.00	Banti's disease
2.50	27	60	55	110	1.20	8.32	54	15.6	31.3	0.99	30.1	0.90	von Jaksch's anemia
3.55	29	64	42	84	0.90	8.78	57*	12.3	24.6	0.80	26.7	0.80	Banti's disease
3.92	37	81	48	96	1.03	11.08	72	13.8	27.7	0.90	29.7	0.89	Chronic hemolytic jaundice
4.37	33	71	38	76	0.80	9.40	61*	10.6	21.2	0.69	29.0	0.86	Banti's disease
						Summary							
2.69	26	56	48	96	1.04	7.70	50	14.3	28.6	0.93	29.7	0.89	Average in 15 cases

* Determination made by means of the hemoglobinometer.

TABLE 5.—*Determinations of a Qualitative Defect in Blood Formation*

Red Blood Cells per Cu.Mm., Millions	Packed Red Cells: Hematocrit Reading per 100 Cc., in Cc.	Packed Red Cells: Per Cent of Normal	Packed Red Cells: Volume Coefficient, Cc.	Mean Corpuscular Volume, Cubic Microns	Volume Index	Hemoglobin: Gm. per 100 Cc.	Hemoglobin: Per Cent of Normal	Hemoglobin: Hemoglobin Coefficient, Gm.	Mean Corpuscular Hemoglobin, Micromicrograms	Color Index	Mean Corpuscular Hemoglobin, Concentration, per Cent	Saturation Index	Diagnosis
						Typical Determinations							
1.60	15	33	47	94	1.03	4.17	27	13.8	27.6	0.90	29.1	0.87	Chronic nephritis
1.69	14	31	42	84	0.91	3.54	23	10.5	21.0	0.68	25.1	0.75	Cancer of the uterus
1.97	18	39	45	90	0.99	4.62	30	11.5	23.1	0.75	25.7	0.77	Malnutrition
2.01	19	42	47	94	1.02	6.47	42	15.7	31.4	1.02	33.5	1.00	Chronic nephritis
2.04	18	40	45	90	0.98	6.17	29	10.8	21.5	0.70	24.1	0.72	Achlorhydria
2.10	20	44	48	96	1.05	5.24	34	12.5	25.0	0.81	25.7	0.77	Malnutrition
2.14	17	37	40	80	0.86	3.54	23	8.2	16.3	0.53	20.8	0.62	Dietary deficiency
2.24	21	46	47	94	1.02	6.00	39	13.6	27.1	0.88	28.7	0.86	Cancer of the colon
2.26	21	46	47	94	1.02	7.10	46	15.7	31.4	1.02	33.5	1.00	Focal infection
2.52	23	50	46	92	1.00	5.70	37	11.4	22.8	0.74	24.8	0.74	Achlorhydria
2.67	24	52	45	90	0.98	6.78	44	12.6	25.3	0.82	28.4	0.85	Chronic bronchitis
2.83	25	54	44	88	0.95	6.00	39	10.5	21.0	0.68	24.1	0.72	Cancer of the cervix
2.85	19	42	34	68	0.74	4.62	30	8.2	16.3	0.53	23.8	0.71	Anemia of pregnancy
3.10	28	61	46	92	0.99	7.85	51	12.8	25.5	0.83	27.4	0.82	Deficiency disease
3.14	25	54	40	80	0.86	6.47	42	10.2	20.5	0.67	26.0	0.78	Anemia of pregnancy
3.21	30	65	47	94	1.01	8.00	52	12.5	25.0	0.81	26.7	0.80	Lead poisoning
3.27	34	73	51	102	1.10	10.00	65	15.4	30.8	1.00	30.1	0.90	Subpectoral abscess
3.31	28	61	42	84	0.92	7.70	50	14.2	28.3	0.76	27.7	0.83	Cancer of the stomach
3.40	32	70	47	94	1.03	10.00	65	14.8	29.6	0.96	31.1	0.93	Myxedema
3.40	27	59	40	80	0.87	7.55	49	11.1	22.2	0.72	27.7	0.83	Oral sepsis
3.45	31	67	45	90	0.97	9.25	60	13.4	26.8	0.87	30.1	0.90	Chronic cholecystitis
3.50	29	63	41	82	0.90	9.70	63	13.9	27.7	0.90	33.5	1.00	Cirrhosis of the liver
3.50	31	67	44	88	0.95	10.00	65	14.3	28.6	0.93	32.4	0.97	Deficiency disease
3.64	34	73	46	92	1.00	10.30	67	14.2	28.3	0.92	30.7	0.92	Achlorhydria
3.71	30	65	41	82	0.88	6.00	39	8.8	17.6	0.57	20.1	0.60	Ochronosis
4.11	39	85	48	96	1.04	12.00	82	14.5	29.0	1.00	32.1	0.96	Cancer of the colon
4.19	34	75	41	82	0.89	7.40	48	8.8	17.6	0.57	21.4	0.64	Achlorhydria
4.61	44	95	47	94	1.03	12.30	80	13.4	26.8	0.87	28.4	0.85	Chlorosis
5.26	30	66	29	58	0.63	6.93	45*	6.5	12.9	0.42	22.8	0.68	Achlorhydria
5.96	37	80	31	62	0.67	9.40	61*	7.9	15.7	0.51	25.4	0.76	Hypothyroidism
						Summary in 110 cases							
3.46	27	59	39	78	0.86	8.2	53	11.9	23.7	0.77	30.1	0.90	

* Determination made by means of the hemoglobinometer.

The anemias due to defective blood formation make up by far the largest group (table 5). The pernicious anemia group is summarized separately. In table 5 are shown the typical determinations in 30 cases of anemia other than pernicious anemia due to a depression of bone marrow formation. These anemias vary greatly; in many there is relatively little change in the cell volume; in others, especially with a high red cell count, there is a great decrease in cell volume. A color index within normal limits is seldom found in this group, and the saturation index is usually well below normal. In this entire group only 4 patients, other than those suffering from pernicious anemia, had a mean corpuscular volume greater than 1. The clinical diagnoses were anemia due to infection of the arm following vaccination, cancer of the stomach, cancer of the colon and von Jaksch's anemia. The average red cell

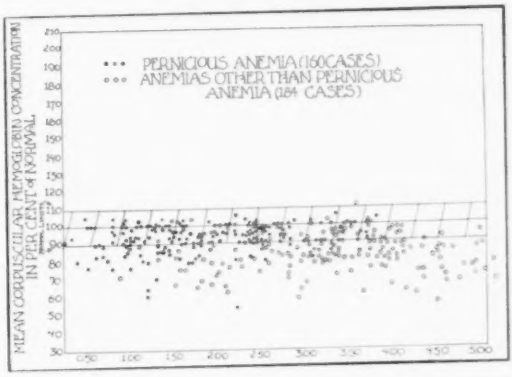
PERNICIOUS ANEMIA (160 CASES)
ANEMIAS OTHER THAN PERNICIOUS ANEMIA (184 CASES)
MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION IN PER CENT of NORMAL

Fig. 6.—The mean corpuscular hemoglobin concentration in pernicious anemia contrasted with that in other types of anemia. The hemoglobin concentration is never above the normal limit.

count was 3.46 millions, the volume index 0.86, corresponding to a mean corpuscular volume of 78 cubic microns, the color index 0.77, indicating a mean corpuscular hemoglobin of 23.7 micromicrograms of hemoglobin per cell, and the saturation index 0.90, which is equivalent to a hemoglobin concentration of 30.1 per cent. The lowest volume index was 0.63, the lowest color index 0.37 and the lowest saturation index 0.60. The red cell count varied from 1.60 to 5.96 million.

During the period of this study 160 cases of pernicious anemia have been seen. The determinations in 20 patients with widely varying red cell counts are shown in table 6. The average count for the entire series was 1.85 millions, the volume index 1.43 (mean corpuscular volume, 132 cubic microns), the color index 1.31 (mean corpuscular hemoglobin, 40.4 micromicrograms), and the saturation index 0.91

TABLE 6.—*Determinations in Pernicious Anemia*

Red Blood Cells per Cu.Mm., Millions	Packed Red Cells: Hematocrit Reading per 100 Cc., in Cc.	Packed Red Cells: Per Cent of Normal	Packed Red Cells: Volume Coefficient, Cc.	Mean Corpuscular Volume, Cubic Microns	Volume Index	Hemoglobin: Gm. per 100 Cc.	Hemoglobin: Per Cent of Normal	Hemoglobin: Hemoglobin Coefficient, Gm.	Mean Corpuscular Hemoglobin, Micromicrograms	Color Index	Mean Corpuscular Hemoglobin Concentration, per Cent	Saturation Index
					Typical Determinations							
0.40	6.9	15	76	152	1.66	1.8	12	20.4	40.8	1.33	27.0	0.80
0.53	7.8	17	74	148	1.60	2.5	16	25.8	51.6	1.68	35.3	1.05
0.59	7.8	17	65	130	1.42	2.6	17	21.8	43.6	1.42	33.7	1.00
0.66	9.7	21	75	150	1.62	3.2	21	25.0	50.0	1.62	33.7	1.00
0.73	12.0	27	83	166	1.80	3.7	24	24.6	49.2	1.60	30.0	0.89
0.80	15.0	32	92	184	2.00	3.9	26	25.0	50.0	1.62	27.1	0.81
1.00	11.5	25	58	116	1.25	3.2	21	16.2	32.4	1.05	28.4	0.84
1.05	17.0	38	83	166	1.81	5.9	38	27.9	55.8	1.81	33.7	1.00
1.14	16.0	35	70	146	1.52	5.4	35	23.4	46.8	1.52	33.7	1.00
1.20	15.0	33	63	126	1.38	4.6	30	19.3	38.6	1.25	30.7	0.91
1.39	20.0	44	71	142	1.56	6.0	39	21.4	42.8	1.39	29.6	0.88
1.41	18.5	40	65	130	1.43	6.0	39	21.4	42.8	1.39	33.0	0.98
1.55	22.0	48	70	140	1.52	7.1	46	22.8	45.6	1.48	32.4	0.96
1.75	21.0	46	64	128	1.38	5.8	38	16.9	33.8	1.10	26.7	0.79
2.10	27.0	58	62	124	1.35	8.5	55	20.0	40.0	1.30	32.4	0.96
2.25	27.0	58	59	118	1.29	8.5	55	18.8	37.6	1.22	32.0	0.95
2.40	29.0	63	60	120	1.30	9.2	60	19.3	39.6	1.25	32.4	0.96
2.88	39.0	85	67	134	1.46	11.9	77	20.4	40.8	1.33	30.7	0.91
3.10	35.0	75	56	112	1.21	11.7	76	19.0	38.0	1.23	34.3	1.02
3.60	43.0	94	60	120	1.29	14.5	94	19.9	39.8	1.29	33.7	1.00
					Summary of 160 cases							
1.85	25.0	53	66	132	1.43	7.4	48	20.2	40.4	1.31	30.7	0.91

TABLE 7.—*Determinations in Anemia Due to a Quantitative Defect in Blood Formation*

Red Blood Cells per Cu.Mm., Millions	Packed Red Cells: Hematocrit Reading per 100 Cc., in Cc.	Packed Red Cells: Per Cent of Normal	Packed Red Cells: Volume Coefficient, Cc.	Mean Corpuscular Volume, Cubic Microns	Volume Index	Hemoglobin: Gm. per 100 Cc.	Hemoglobin: Per Cent of Normal	Hemoglobin: Hemoglobin Coefficient, Gm.	Mean Corpuscular Hemoglobin, Micromicrograms	Color Index	Mean Corpuscular Hemoglobin, Concentration, per Cent	Saturation Index	Diagnosis
						Typical Determinations							
1.49	14	31	47	94	1.03	4.62	30	15.4	30.8	1.00	32.4	0.97	Acute myeloid leukemia
1.52	14	31	46	92	1.00	4.94	32	15.9	31.8	1.03	33.5	1.03	Osteitis fibrosa cystica
1.61	15	30	46	92	1.00	3.54	23	11.5	23.1	0.75	25.0	0.75	Aleukemic leukemia
2.50	21	47	43	86	0.94	7.24	47	14.5	29.0	0.94	33.5	1.00	Leukemia
2.58	30	66	43	86	0.94	7.80	51*	15.2	30.4	0.99	26.0	0.77	Multiple myeloma
2.63	24	54	47	94	1.02	7.70	50	14.5	29.0	0.90	30.7	0.92	Monocytic leukemia
						Summary							
2.10	20	43	47	94	1.02	6.00	39	14.3	28.6	0.93	30.4	0.91	Average in 6 cases

* Determination made by means of the hemoglobinometer.

(mean corpuscular hemoglobin concentration, 30.7 per cent). The lowest volume index was 1.13 and the highest 2.24; the lowest color index was 0.80 and the highest 1.87. The saturation index was never over 1.00 beyond the limits of error.

The one constant feature of the blood in pernicious anemia is the macrocytosis, as shown by the increased volume index. In the active cases the mean cell volume is well increased although it tends to be higher with the relatively low counts. Sixty per cent of the cell counts in pernicious anemia are below 2.0 millions while only 14 per cent of the other types of anemia are below 2.0 millions. I have reported elsewhere [19] the correlation of the gastric analysis and the macrocytosis of the red cells in the diagnosis of pernicious anemia. I have seen no

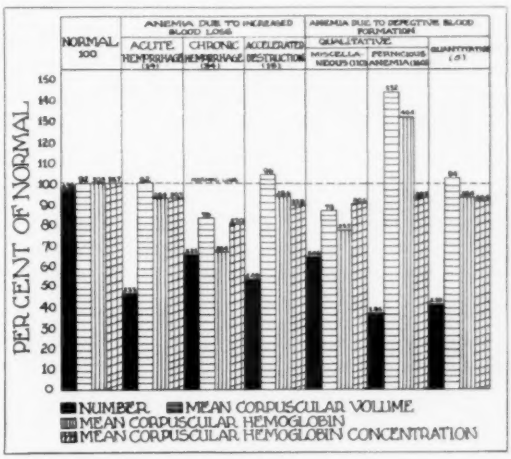

Fig. 7.—Erythrocyte constants (number, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration) in the different clinical groups of anemia.

untreated patient with an active case of pernicious anemia without a macrocytosis or with free hydrochloric acid in the gastric contents. A patient having a plus volume index with an achlorhydria practically without exception has pernicious anemia. The diagnosis of an untreated pernicious anemia in the absence of these two criteria is always open to question. On the other hand, macrocytosis is seldom seen except in pernicious anemia. Exceptions are seen in the acute anemia of pregnancy, some parasitic anemias and the hemolytic anemias due to hemolytic jaundice and to toxins.

19. Haden, R. L.: Macrocytosis of the Erythrocytes and Achlorhydria in Pernicious Anemia, J. A. M. A. **98**:202 (Jan. 16) 1932.

* Determination made by means of the hemoglobinometer.

TABLE 8.—*Determinations in Polycythemia*

Red Blood Cells per Cu. Mm., Millions	Packed Red Cells: Hematocrit Reading per 100 Cc., in Cc.	Packed Red Cells: Per Cent of Normal	Packed Red Cells: Volume Coefficient, Cc.	Mean Corpuscular Volume, Cubic Microns	Volume Index	Hemoglobin: Gm. per 100 Cc.	Hemoglobin: Per Cent of Normal	Hemoglobin: Hemoglobin Coefficient, Gm.	Mean Corpuscular Hemoglobin, Micromicrograms	Color Index	Mean Corpuscular Hemoglobin Concentration, per Cent	Saturation Index
					Typical Determinations							
6.09	52	113	42	84	0.92	18.79	122*	15.4	30.8	1.00	36.5	1.00
6.12	58	126	47	94	1.03	16.8	109*	13.6	27.2	0.88	29.3	0.87
6.90	66	144	48	96	1.04	21.6	140*	15.5	31.0	1.01	32.7	0.97
8.16	74	160	45	90	0.98	24.6	160	14.9	29.8	0.98	33.7	1.00
9.60	74	160	38	76	0.83	22.8	148	12.0	24.0	0.78	31.4	0.93
					Summary of 5 cases							
7.37	65	141	44	88	0.96	20.9	136	14.2	28.4	0.92	32.7	0.97

* Determination made by means of the hemoglobinometer.

TABLE 9.—*Summary of Determinations in Four Hundred and Forty-Four Cases*

Group	No.	Red Blood Cells per Cu. Mm., Millions	Packed Red Cells: Hematocrit Reading per 100 Cc., in Cc.	Packed Red Cells: Per Cent of Normal	Packed Red Cells: Volume Coefficient, Cc.	Mean Corpuscular Volume, Cubic Microns	Volume Index	Hemoglobin: Gm. per 100 Cc.	Hemoglobin: Per Cent of Normal	Hemoglobin: Hemoglobin Coefficient, Gm.	Mean Corpuscular Hemoglobin, Micromicrograms	Color Index	Mean Corpuscular Hemoglobin Concentration, per Cent	Saturation Index
Normal	100	4.78	43.7	95	46	92	1.00	14.8	95	15.4	30.8	1.00	33.7	1.00
Acute hemorrhage	14	2.33	22.0	47	46	92	1.00	6.6	43	14.2	28.4	0.92	30.7	0.92
Chronic hemorrhage	34	3.25	25.0	54	38	76	0.83	6.6	43	10.2	20.4	0.66	27.0	0.80
Accelerated destruction	15	2.69	26.0	56	48	96	1.04	7.7	50	14.3	28.6	0.93	29.7	0.89
Defective formation (qualitative)	110	3.46	27.0	59	39	78	0.86	8.2	53	11.9	23.7	0.77	30.1	0.90
Pernicious anemia	160	1.85	25.0	53	66	132	1.43	7.4	48	20.2	40.4	1.31	30.7	0.91
Defective formation (quantitative)	6	2.10	20.0	43	47	94	1.02	6.0	39	14.3	28.6	0.93	30.4	0.91
Polycythemia	5	7.37	65.0	141	44	88	0.96	20.9	136	14.2	28.4	0.92	32.7	0.97

The anemias due to a quantitative defect in blood formation are relatively few. The group that I have studied are summarized in table 7. Here the cell volume and hemoglobin content are relatively normal as one would expect. It is always difficult to know just what cases to put in this group. In leukemia, while there is a decrease in red cell forming tissue by the infiltration, there may be also a depression of bone marrow formation secondary to the toxemia characteristic of the disease.

The determinations in a small group of polycythemia vera are shown in table 8. The cell volume was normal in 4 cases. In one with a count of 9.60 millions, the volume index was 0.83 and the color index was 0.78. In the others the color index was relatively normal and the saturation index was normal in all. It is probable that the percentage by volume of packed cells cannot exceed 75; therefore if the cell count is above 7.50 millions, the mean corpuscular volume necessarily decreases.

The determinations in the 444 cases reported here are summarized in table 9, and in figures 4, 5, 6 and 7. From the standpoint of classification the important points are:

1. There is a relatively slight change in mean cell volume and hemoglobin content in the acute anemia of hemorrhage or in quantitative defects in blood formation. Here there is a decrease in the number of cells, but the cells remaining are relatively normal.

2. There is a marked decrease in cell volume and hemoglobin content with long-continued mechanical blood loss. As the bone marrow is depleted, the cells become smaller with a low hemoglobin content.

3. In anemia due to accelerated blood destruction there is a tendency to macrocytosis. Most of the cases in this group show an increase in reticulocytes, which are larger than normal; hence the mean cell volume is greater than normal. This is not a constant observation, however.

4. In pernicious anemia macrocytosis is constant and marked.

5. In polycythemia the cell volume is unchanged until the count is high, at which time the cells become smaller.

VALUE OF THE VOLUME AND HEMOGLOBIN CONTENT IN PROGNOSIS

In pernicious anemia a persistence of macrocytosis in spite of adequate treatment is a very unfavorable sign, since the macrocytosis is evidence of a lack of some principle necessary for normal blood formation. This is an unusual observation, but is made occasionally.

In other types of anemia the greater the decrease in average cell volume the greater is the depletion of bone marrow and the longer the

time required for the return of the blood to normal. For instance, one expects more rapid and satisfactory results from treatment in a patient with a cell count of 3.0 millions, a volume index of 1.00 and a hemoglobin content of 30 per cent than in a patient with the same

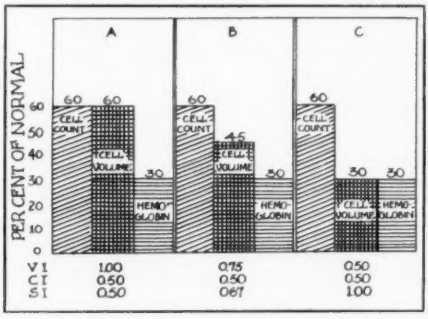

Fig. 8.—Relation of hemoglobin to cell volume with constant red cell count and hemoglobin but a varying volume of packed cells. In *A* the red cells are of normal size and half filled with hemoglobin, so that they have only to be filled with hemoglobin in order to return to normal; in *B* the cells are three-fourths normal size and two-thirds filled with hemoglobin; in *C* the cells are only half the normal size, but are filled with hemoglobin, so that both the cell mass and the hemoglobin must be increased to return to normal.

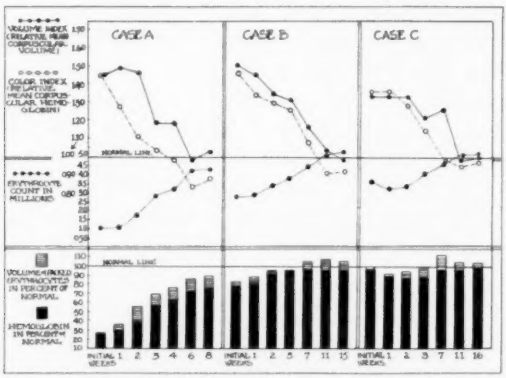

Fig. 9.—Changes in erythrocytes in three patients with pernicious anemia who have had adequate liver treatment. Note the simultaneous return to the normal line of the count and mean corpuscular volume.

cell count and hemoglobin content but with a volume index of 0.65. There are two reasons for this. The small cells indicate marked bone marrow depletion and hence a more serious state of the blood-forming tissue, and the hemoglobin cannot be increased until the cell volume is

TABLE 10.—*Determinations in Patients with Pernicious Anemia Adequately Treated with Liver or Liver Substitutes*

Case	Weeks	Red Blood Cells per Cu.Mm., Millions	Packed Red Cells			Mean Corpuscular Volume, Cubic Microns	Volume Index	Hemoglobin			Mean Corpuscular Hemoglobin, Micromicrograms	Color Index	Mean Corpuscular Hemoglobin Concentration, per Cent	Saturation Index
			Hematocrit Reading per 100 Cc., in Cc.	Per Cent of Normal	Volume Coefficient, Cc.			Gm. per 100 Cc.	Per Cent of Normal	Hemoglobin Coefficient, Gm.				
A	0	1.10	13	29	66	132	1.45	4.49	29	22.3	44.7	1.45	33.7	1.00
	1	1.18	16	35	68	136	1.48	4.62	30	19.6	39.2	1.27	29.0	0.86
	2	1.80	24.5	53	67	134	1.47	6.16	40	17.1	34.2	1.11	25.3	0.75
	3	2.82	32	69	55	110	1.19	8.95	58	16.0	32.0	1.04	28.3	0.83
	4	3.15	35	75	55	110	1.19	9.40	61	15.1	30.2	0.98	27.4	0.81
	6	4.26	38.5	84	46	92	0.99	10.95	71	12.9	25.8	0.84	28.7	0.85
	8	4.27	40.5	88	47	94	1.03	11.55	75	13.4	26.8	0.87	28.7	0.85
B	0	2.77	38	82	69	138	1.50	12.15	79	22.5	45.0	1.46	32.7	0.97
	1	2.99	40	87	66	132	1.45	12.48	81	20.7	41.4	1.35	31.4	0.93
	2	3.49	44	95	62	124	1.35	14.00	91	20.0	40.0	1.30	32.4	0.96
	3	3.79	46	100	60	120	1.32	14.80	96	19.6	39.2	1.27	32.4	0.96
	7	4.48	48	104	54	108	1.17	14.95	97	....	....	1.08	31.4	0.93
	11	5.13	49	106	47	94	1.03	14.48	94	14.0	28.0	0.91	30.3	0.90
	15	5.23	48	104	46	92	0.99	14.95	97	14.2	28.4	0.92	31.4	0.93
C	0	3.56	45	98	62	124	1.35	15.10	98	20.7	41.4	1.35	33.7	1.00
	1	3.33	41	89	62	124	1.34	14.00	91	21.1	42.2	1.37	34.7	1.03
	2	3.47	43	93	61	122	1.33	14.00	91	19.9	39.8	1.29	33.0	0.98
	3	4.09	46	100	56	112	1.22	14.48	94	17.7	35.4	1.15	31.7	0.94
	7	4.92	51	111	57	114	1.26	14.95	97	15.1	30.2	0.98	29.3	0.87
	11	5.11	47	102	46	92	1.00	14.95	97	14.5	29.0	0.95	32.0	0.95
	16	5.15	48	104	47	94	1.01	15.40	100	14.9	29.8	0.97	32.4	0.96

TABLE 11.—*Determinations in Patients with Pernicious Anemia Inadequately or Not Treated with Liver*

Case	Weeks	Red Blood Cells per Cu.Mm., Millions	Packed Red Cells			Mean Corpuscular Volume, Cubic Microns	Volume Index	Hemoglobin			Mean Corpuscular Hemoglobin, Micromicrograms	Color Index	Mean Corpuscular Hemoglobin Concentration, per Cent	Saturation Index
			Hematocrit Reading per 100 Cc., in Cc.	Per Cent of Normal	Volume Coefficient, Cc.			Gm. per 100 Cc.	Per Cent of Normal	Hemoglobin Coefficient, Gm.				
D	0	0.69	9.7	21	70	140	1.52	3.08	20	22.3	44.6	1.45	32.0	0.95
	2	1.00	11.5	25	58	116	1.25	2.93	19	14.6	29.2	0.95	26.3	0.78
	3	1.62	21.0	46	65	130	1.42	5.85	38	18.0	36.0	1.17	27.9	0.82
	4	2.03	23.6	50	58	116	1.24	7.10	46	17.5	35.0	1.14	31.0	0.92
	6	2.82	37.0	80	63	126	1.37	10.70	67	17.7	35.4	1.15	28.3	0.84
	65	2.51	32.0	70	64	128	1.40	9.55	62	19.0	38.0	1.23	30.0	0.89
E	0	2.46	33.0	71	68	137	1.49	10.05	68	21.9	43.8	1.42	32.4	0.96
	12	3.66	40.0	87	55	109	1.19	11.55	75	15.9	31.8	1.03	29.0	0.86
	16	3.72	44.0	96	60	120	1.30	12.15	79	16.1	32.2	1.05	27.9	0.82
	22	3.32	46.0	100	69	138	1.50	12.61	82	19.1	38.2	1.24	27.9	0.82
	26	2.52	35.6	75	68	136	1.48	11.22	73	22.2	44.4	1.44	30.0	0.88
	30	2.42	38.5	83	78	157	1.71	12.31	80	25.4	50.8	1.65	32.4	0.96
	46	2.60	32.0	70	62	124	1.34	10.70	67	19.7	39.4	1.18	32.4	0.96
	60	2.94	42.0	92	71	143	1.56	15.21	86	22.5	45.0	1.46	31.4	0.93
F	0	1.83	25.0	54	67	134	1.46	7.40	48	20.2	40.4	1.30	30.0	0.89
	4	3.42	38.5	84	56	112	1.22	12.15	79	18.3	36.7	1.16	32.7	0.97
	8	3.31	30.0	65	45	91	0.99	10.00	65	15.3	30.5	0.99	33.7	1.00
	12	2.50	29.0	63	58	116	1.26	8.95	58	18.4	36.7	1.16	32.0	0.95
	20	3.12	32.0	70	52	104	1.13	11.10	72	18.4	36.7	1.16	34.7	1.03
	30	2.70	36.0	77	66	132	1.43	11.10	72	20.5	41.0	1.33	31.7	0.94
	42	2.65	32.0	69	60	120	1.30	10.05	66	20.8	41.6	1.35	32.7	0.97
	62	1.06	23.0	50	111	222	2.40	7.25	47	34.5	69.0	2.24	31.7	0.94
	63	2.06	30.0	65	71	142	1.55	9.55	62	22.7	45.5	1.48	32.7	0.97
	65	3.20	36.0	77	55	110	1.20	11.40	74	18.3	36.7	1.16	32.0	0.95
	69	4.02	44.0	96	55	110	1.20	14.00	91	17.6	35.1	1.14	32.0	0.95
	81	4.50	41.0	90	46	92	1.00	12.31	80	13.7	27.4	0.89	30.0	0.89

increased. The formation of stroma, or hemoglobin-carrying substance, must precede the formation of hemoglobin. This point is illustrated in figure 8.

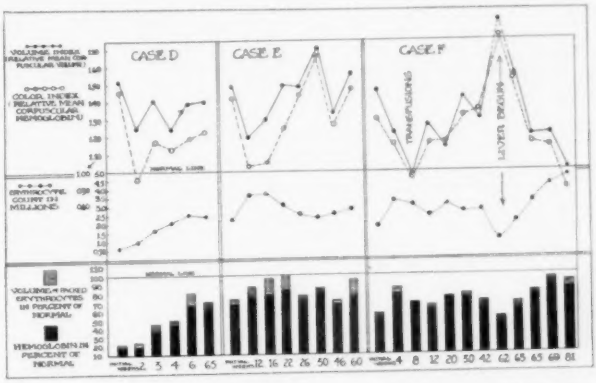

Fig. 10.—Changes in erythrocytes in three patients with pernicious anemia who have had inadequate or no liver treatment. Note that the cell count remains below normal and the mean corpuscular volume constantly above the normal line.

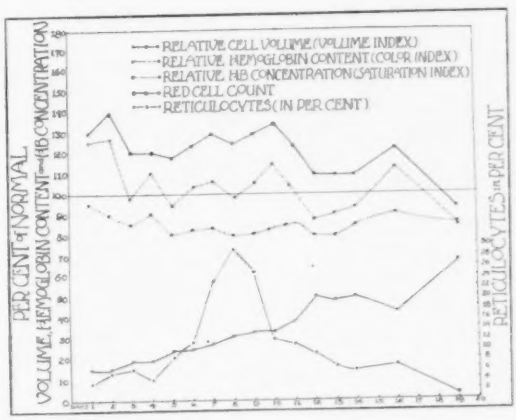
RELATIVE CELL VOLUME (VOLUME INDEX)
RELATIVE HEMOGLOBIN CONTENT (COLOR INDEX)
RELATIVE HB CONCENTRATION (SATURATION INDEX)
RED CELL COUNT
RETICULOCYTES (IN PER CENT)
PER CENT of NORMAL
VOLUME, HEMOGLOBIN CONTENT—HB CONCENTRATION
RETICULOCYTES in PER CENT

Fig. 11.—Daily determinations of the erythrocyte constant in a patient with pernicious anemia who has had adequate liver treatment.

THE VOLUME AND HEMOGLOBIN CONTENT AS AN INDEX OF THERAPY

With the newer methods of treatment for pernicious anemia the blood will return to normal. As the red cell count rises to normal, the mean corpuscular volume indicated by the volume index falls; so the

TABLE 12.—*Daily Determinations in a Patient with Pernicious Anemia Adequately Treated with Liver*

Days	Red Blood Cells per Cu.Mm., Millions	Packed Red Cells			Mean Corpuscular Volume, Cubic Microns	Volume Index	Hemoglobin			Mean Corpuscular Hemoglobin, Micromicrograms	Color Index	Mean Corpuscular Hemoglobin Concentration, per Cent	Saturation Index	Reticulocytes
		Hematocrit Reading per 100 Cc., in Cc.	Per Cent of Normal	Volume Coefficient, Cc.			Gm. per 100 Cc.	Per Cent of Normal	Hemoglobin Coefficient, Gm.					
0	0.81	9.7	21	60	120	1.31	3.08	20	20.8	41.6	1.26	32.0	0.95	3.6
1	0.76	9.7	21	67	134	1.46	2.93	19	22.3	44.6	1.27	30.3	0.90	5.6
2	0.97	10.2	22	56	113	1.22	2.93	19	15.1	30.2	0.98	29.0	0.86	6.0
3	0.94	10.5	23	56	112	1.21	3.24	21	17.1	34.2	1.11	30.7	0.91	4.2
4	1.14	12.0	27	55	109	1.18	3.40	22	14.8	29.6	0.96	27.4	0.81	8.4
5	1.27	14.0	31	57	114	1.24	3.86	26	15.7	51.4	1.04	28.3	0.83	11.2
6	1.34	16.0	35	60	120	1.30	4.47	29	16.5	33.0	1.07	28.3	0.83	23.4
7	1.58	18.5	40	57	115	1.25	4.94	32	15.4	30.8	1.00	27.0	0.80	29.8
8	1.65	19.5	43	60	125	1.30	5.40	35	16.1	32.2	1.06	27.4	0.81	25.0
9	1.67	21.5	45	62	124	1.35	5.85	38	17.7	35.4	1.15	28.4	0.84	12.0
10	1.93	22.0	48	57	114	1.24	6.16	40	15.9	31.8	1.03	29.0	0.86	11.0
11	2.56	26.0	56	55	111	1.10	6.95	45	13.7	27.4	0.89	27.0	0.80	9.0
12	2.45	25.0	54	55	111	1.10	6.95	45	14.0	28.0	0.91	27.0	0.80	6.6
13	2.57	26.0	56	55	111	1.10	7.40	48	29.0	58.0	0.94	28.7	0.85	6.2
15	2.19	26.0	56	57	114	1.27	8.00	52	18.1	36.2	1.18	31.1	0.92	7.0
18	3.43	30.0	65	43	86	0.94	8.95	58	12.9	25.8	0.84	29.0	0.86	1.6
24	3.33	34.0	73	55	111	1.10	10.02	65	14.9	29.8	0.97	30.0	0.89	1.6
26	3.65	36.0	77	48	97	1.05	10.80	70	14.8	29.6	0.96	30.3	0.90	1.6

TABLE 13.—*Determinations in a Patient with Simple Achlorhydric Anemia Adequately Treated with Iron*

Weeks	Red Blood Cells per Cu.Mm., Millions	Packed Red Cells			Mean Corpuscular Volume, Cubic Microns	Volume Index	Hemoglobin			Mean Corpuscular Hemoglobin, Micromicrograms	Color Index	Mean Corpuscular Hemoglobin Concentration, per Cent	Saturation Index
		Hematocrit Reading per 100 Cc., in Cc.	Per Cent of Normal	Volume Coefficient, Cc.			Gm. per 100 Cc.	Per Cent of Normal	Hemoglobin Coefficient, Gm.				
0	5.02	35	66	32	64	0.66	7.55	49	7.55	15.0	0.49	23.6	0.70
1	5.95	41	89	35	70	0.74	9.40	61	8.00	16.0	0.52	22.6	0.67
2	5.80	42	91	36	72	0.78	10.95	71	9.40	18.8	0.61	26.3	0.78
3	6.16	46	100	37	74	0.81	11.70	78	9.70	19.4	0.63	26.3	0.78
4	5.63	46	100	41	82	0.88	11.70	78	10.61	21.2	0.69	26.3	0.78
5	5.66	48	104	42	84	0.92	14.91	84	11.40	22.8	0.74	28.3	0.83
6	6.00	50	109	31	62	0.91	14.00	91	11.70	23.4	0.76	28.3	0.83
7	5.87	48	104	41	82	0.88	14.00	91	11.85	23.7	0.77	29.3	0.87
9	5.66	49	106	44	88	0.95	14.00	91	12.50	25.0	0.81	29.3	0.87
11	5.56	48	104	43	86	0.94	14.00	91	12.35	24.7	0.80	29.6	0.88
16	5.27	45	97	42	84	0.92	14.00	91	13.25	27.5	0.86	31.4	0.93

lines indicating these two factors converge to a point on the base line. No patient with pernicious anemia is adequately and satisfactorily treated until the volume index has returned to normal. The aim of treatment is the relief from the anemia and the prevention of subacute combined degeneration of the spinal cord. The persistence of the anemia or the development of a cord lesion is the best of evidence that the deficiency responsible for the disease is not properly supplied. Since the advent of liver therapy, patients have been constantly seen who have taken enough liver to improve the anemia but not enough to return the blood to normal. In such patients a macrocytosis persists and usually a cord lesion develops during the period of treatment.

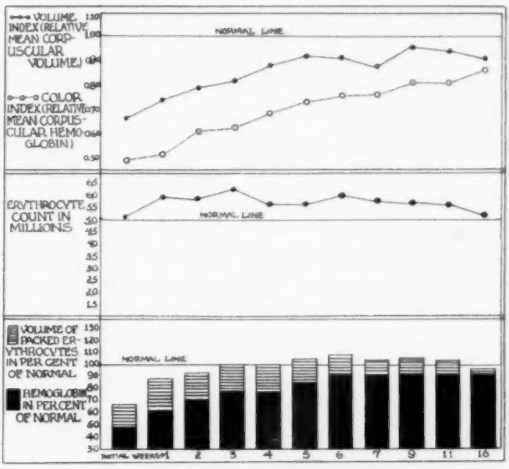
VOLUME INDEX (RELATIVE MEAN CORPUSCULAR VOLUME)
COLOR INDEX (RELATIVE MEAN CORPUSCULAR HEMOGLOBIN)
NORMAL LINE
ERYTHROCYTE COUNT IN MILLIONS
NORMAL LINE
VOLUME OF PACKED ERYTHROCYTES IN PER CENT OF NORMAL
HEMOGLOBIN IN PER CENT OF NORMAL
NORMAL LINE
INITIAL WEEKS 1 2 3 4 5 6 7 9 11 16

Fig. 12.—Changes in erythrocytes in a patient with simple achlorhydric anemia treated only with Blaud's mass pills (60 grains [3.8 Gm.] daily). Note the relative constancy of the count while there is a gradual increase in the mean corpuscular volume. The cell mass increases greatly and is finally almost completely filled with hemoglobin.

In a general way the color index follows the volume index, but the color index may fall to normal with a persistence of the macrocytosis.

In table 10 are shown the determinations in a group of patients who showed the characteristic response to adequate liver therapy. This is illustrated in figure 9. The determinations in a group of patients who did not receive liver therapy or who received insufficient liver therapy are shown in table 11 and figure 10. The determinations in a single patient with daily blood studies are shown in table 12 and figure 11. In the case of every patient suffering from pernicious anemia a care-

ful blood study should be made at regular intervals to see that the volume index has returned to normal and has remained normal.

In other types of anemia the aim of treatment is also to return the blood to normal. Here also careful studies of cell volume and size are valuable as an index of treatment. In simple achlorhydric anemia and other types of anemia that respond to adequate iron therapy, a study of the cell volume may give some interesting information concerning the action of iron in such conditions. The therapeutic action of iron in anemia has been related largely to the hemoglobin. In table 13 and figure 12 are shown the successive observations on the blood in a patient who received adequate iron therapy. There was a great increase in the volume of packed cells as well as in hemoglobin. These data would indicate that iron causes an increase in stroma as well as in hemoglobin.

SUMMARY

1. The accurate determination of the volume, hemoglobin content and hemoglobin concentrations of the erythrocyte is a relatively simple procedure and should be carried out in every case of anemia that requires careful study.

2. The results are best expressed as indexes rather than in absolute figures. The indexes express the absolute values relative to normal.

3. In normal men and women the indexes are always within the limits of normal (0.90 and 1.10).

4. Every case of anemia that warrants thorough study should be classified on the basis of the number, the volume and the hemoglobin content of the red blood cells.

5. A simple classification and terminology on the foregoing basis is suggested.

6. The typical determinations in different clinical groups of anemia are reported.

7. In the case of acute mechanical blood loss there is a change in the number of cells only; in chronic loss the cells become progressively smaller, with a low hemoglobin content.

8. If the anemia is due to accelerated destruction, the mean cell volume tends to increase since the reticulocytes are usually larger than normal.

9. With decreased blood formation the determinations are very variable. The mean cell volume and hemoglobin content are seldom greater than normal except in pernicious anemia.

10. In pernicious anemia an increase in volume and hemoglobin content is the most characteristic observation on the blood.

11. The volume and hemoglobin content are important aids in prognosis.

12. In pernicious anemia the mean volume of the erythrocyte is the best index in treatment. If the patient is adequately treated, the mean cell volume returns to normal.

13. In the treatment for other types of anemia the volume and hemoglobin content of the red cell are valuable aids in treatment.

PRIMARY CANCER OF THE LUNG

A CLINICAL AND PATHOLOGIC SURVEY OF FIFTY CASES

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The relative frequency and increasing tendency toward the occurrence of primary cancer of the lung has prompted me to make the following correlation. The clinical data was obtained through the cooperation of the various medical and roentgenologic departments. In reviewing the autopsy records from October, 1929, to November, 1930, 50 cases of primary cancer of the lung were found. The total number of autopsies made during this period was 3,064, the relative frequency of cancer of the lung being, therefore, 1.5 per cent. Deducting the number of autopsies made on persons 30 years of age or under left 2,209. The incidence of cancer of the lung in this group over 30 years was therefore 2.26 per cent.

I shall first consider the clinical aspect of this disease. In an endeavor to find some of the possible etiologic factors, the following observations were made:

Of the group studied, 78 per cent were males and 22 per cent females. From the autopsy records during this period the ratio was 52.5 per cent males to 47.5 per cent females, practically an equal division. The variation in age in the group of 50 patients was from 37 to 77 years, the average being 50.7. Four per cent were between 30 and 40 years of age, 14 per cent between 40 and 50, 48 per cent between 50 and 60, 24 per cent between 60 and 70 and 10 per cent between 70 and 80; 72 per cent of this group were smokers.

A study of environment or occupation proved of little significance. The patients were all born either in Austria or in one of the adjacent countries, and were all from the working class. The number of years spent in large or small communities, factory centers, farming districts, etc., was not obtainable from the existing records. The occupations were varied, and were thirty in number. In only one patient was a history of a chronic cough as a result of his occupation noted. This patient was an upholsterer. The largest number in any one occupation was among the women, 6 being domestic servants. Of the 39 men only 5 could be said to have been subjected to more than the average

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From the Pathologico-Anatomic Institute of the University of Vienna, Prof. R. Maresch, Director.

amount of respiratory irritation, as far as their stated occupations were concerned. Irritating fumes of any sort, with the possible exception of tobacco, did not seem to play a rôle. In the family history the percentage of parents who died of cancer in any part of the body, or of diseases of the lung, was considered. In the past history previous pulmonary or pleural illnesses were noted. In 47 cases in which a family and past history was obtainable, the information given in table 1 was derived.

Of particular interest were the 4 patients in whose histories periodic attacks of high fever, irritating cough, expectoration and accompanying shortness of breath were noted. The expectoration in the early stages was generally small in amount, and increased appreciably as the fever decreased. The attacks usually lasted from two to six weeks, and the patients had been treated in many hospitals. No tubercle bacilli were ever found. The intervals of comparatively good health

TABLE 1.—*History*

	Per Cent
Family history	
Parents who died of cancer	15
Parents who died of pulmonary infection	24
Past history	
Grip; pneumonia; upper respiratory infection	17
Bronchitic or asthmatic attacks	15
Recurrent bronchial stenosis	8
Pleurisy	6
Tuberculous infection	2
Total	48

varied from six months to two years, and sometimes even longer. The attacks lasted over a period of several years, one case dating back as far as 1910. These cases were suggestive of the clinical picture of recurrent bronchial stenosis of an inflammatory nature. At autopsy, in these cases, enlarged chronically inflamed hilar glands were found, more often left-sided, causing a compression of the bronchial wall, or the bronchial wall itself showed chronic inflammatory changes with a resulting narrowing of its lumen.

In the present illness, the range of time from the appearance of the first symptom to the day of death was from two years to one day, the average being seven months and twenty-four days. A tabulation of initial symptoms in the present illness is given in table 2.

A grouping of certain specialized symptoms may be observed in table 3. Loss of weight was one of the frequent complaints, and in many cases was marked. In most cases the early cough was dry, irritative and nonproductive, often coming on in severe attacks. As the illness progressed, the cough became productive and purulent in some cases. The amount of sputum varied periodically, depending on the degree of

bronchial stenosis and on the degree of peripheral bronchiectasis, pneumonic infiltrate or abscess formation. It is interesting to note the high percentage of initial symptoms that were the result of metastases rather than the result of the primary growth. This shows the impossibility of an early diagnosis in a large percentage of the cases.

In considering the physical examination of the chest, I shall not attempt to tabulate the findings because of their great variability, individually or collectively, from day to day or from week to week. In 3 cases no abnormal pulmonary findings were noted. In 2 of these cases early cerebral metastases played the predominant rôle, and no pathologic pulmonary findings were noted on the patients' admission to

TABLE 2.—*Initial Symptoms*

	Per Cent	
Lung: Attacks of coughing	12	
Shortness of breath	14	
Bloody sputum	4	44
Bronchitis	10	
Pain in chest	4	
Pleurisy		12
Nervous: Cerebral	14	
Peripheral	6	
Hoarseness (recurrent nerve palsy)	8	
Bone	6	44
Stomach	8	
Uterine bleeding	2	

TABLE 3.—*Selected Symptoms*

No.		Per Cent
15	Pleurisy	30
11	Bloody sputum	22
9	Hoarseness (recurrent nerve palsy)	18
3	Generalized pain in chest	6
3	Difficulty in swallowing	6
6	No symptoms in chest	12

the hospital. Later examinations of the chest were probably neglected owing to the lack of pulmonary symptoms. In the third case the patient had no pulmonary symptoms, and clinical attention was centered chiefly on the cervical and upper mediastinal glandular involvement. From this group of cases with negative findings one may turn to those in which examination revealed the signs of a moderate to a severe bronchitis or assimilated asthma, with an accompanying degree of emphysema. In cases with more advanced symptoms in the lung, some or all of the following signs were frequently found:

1. The presence of a venous collateral circulation across the anterior wall of the chest.

2. The shrinkage of one side of the thoracic cage, with a decrease in the intercostal spaces and a varying degree of retraction of the supraclavicular fossa.

3. A lesser respiratory movement on the shrunken side.

4. Tracheal deviation toward the affected side.

5. Dulness on percussion as the result of a tumor, atelectasis peripheral to a bronchial occlusion, an existing pneumonia or pleural exudate.

6. Paravertebral dulness as a result of mediastinal involvement or hilar infiltration.

7. Hyperresonance as a compensatory measure in the remaining normal or emphysematous lung tissue.

8. Tympanitic resonance in patients with large cavity formation.

9. A lesser degree of respiratory excursion, amounting to a paralysis and upward retraction of the diaphragm on the affected side.

10. Every possible type of breathing or râle, depending on the existing condition of the underlying lung tissue and bronchial tubes.

11. Frequently a pleural rub.

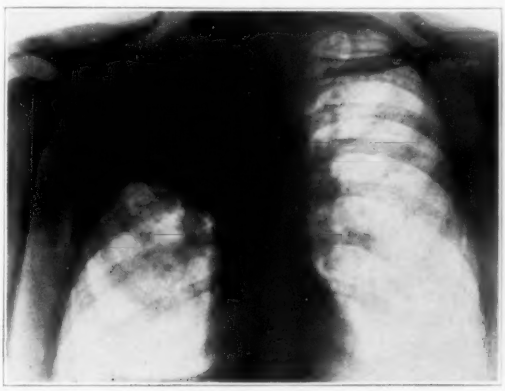

Fig. 1.—Infiltrating process in the right upper lobe with multiple cavities. The trachea is toward the right. The esophageal obstruction is shown by barium sulphate filling. Hilar infiltration is seen. The roentgen diagnosis was: The appearance of lung and esophagus is suggestive of bronchial neoplasm with involvement of the mediastinal glands. Autopsy showed carcinoma of the bronchus of the right upper lobe, first order.

In case of marked pleural effusion the bulging or fulness of the wall of the chest and the deviation of the trachea toward the opposite side overshadowed the tumor picture. These signs varied in number and in intensity, depending on the stage and location of the tumor. I think that at this time the greatest stress is to be laid on the great variability and changeability of the signs in the chest. This multiplicity and variation is due largely to the alternating degree of bronchial stenosis and its effect on the peripheral lung tissue. Therefore, the largest amount of information can be derived only by carefully recording the results of repeated examination of the chest. These findings on physical examination may prove a great diagnostic aid.

During hospitalization, from a moderate to a severe degree of dyspnea was observed in 66 per cent of the cases, terminal dyspnea being omitted. Taken during the period of hospitalization the respiratory range often showed a marked flexibility. In several cases there was a variation of from twelve to fifteen respirations per minute, and in one case, a variation of twenty. This flexibility was largely dependent on the existing degree of bronchial stenosis. In some cases, however, the marked degree of cyanosis with accompanying rapid respiration was

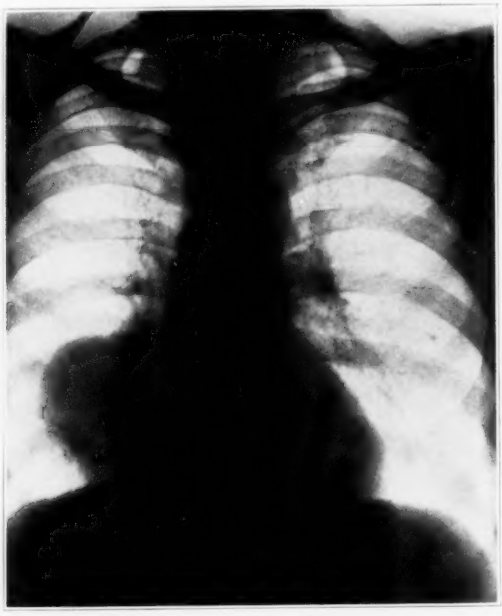

Fig. 2.—Rather sharp-bordered, fist-sized shadow in the right lower lobe. Medial upward fixation of the right side of the diaphragm. The roentgen diagnosis was probable neoplasm of the right lower lobe (echinococcus cysticus?). Autopsy showed carcinoma of the right inferior bronchus, second order.

due to pleural exudate or pressure exerted by mediastinal glands. In the latter group the cyanosis was more likely to be a constant factor and the respiratory rate persistently high. In a few cases during the course of the illness a marked drop in blood pressure was noted. At autopsy these cases showed a bilateral suprarenal involvement.

The period of hospitalization varied from one day to six months and twenty-one days, but the average was one month and fifteen days.

Among the laboratory data I shall first consider the roentgen observations. Roentgenography was found to be the most valuable laboratory

aid in making a correct diagnosis. X-ray plates or fluoroscopic examinations were made of the chest in 40 cases. Of the remaining patients 4 were too weak, and in 6 the metastatic foci presented the dominant symptom; in 2 of these the changes in the lungs were considered to be secondary to a primary growth elsewhere. The presence of a neoplasm was suspected in 72.5 per cent of the cases, if not from the first film, then from a series of films taken at intervals. In only 2 instances were the roentgenologists unable to rule out a tuberculous process. In both of these instances, however, a malignant process was also suspected. Both cases showed upper lobar cavitation.

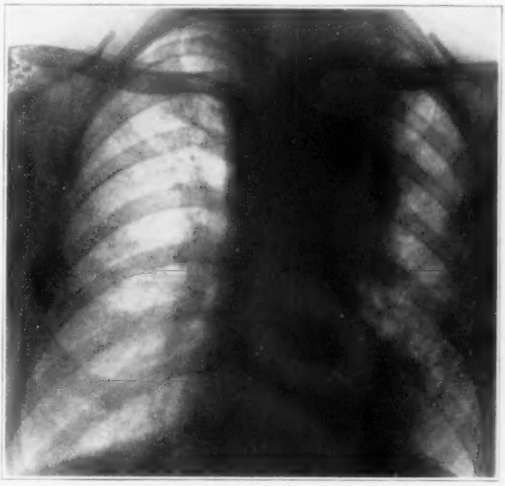

Fig. 3.—A large, unhomogeneous, not sharply bordered shadow extending into the upper left lung field from the hilar region. There is tracheal deviation toward the left. The left side of the diaphragm is high. (By fluoroscopy paradoxical respiration and paralysis of the left side of the diaphragm were demonstrated.) The roentgen diagnosis was probable bronchial carcinoma of the left lung with left-sided phrenic palsy from mediastinal involvement. Autopsy showed left superior bronchial carcinoma, second order.

Some of the findings that lead one to suspect the presence of a malignant process are:

1. Shrinkage of the affected side.
2. The presence of an infiltrating process, most often in the hilar region, showing a marked tendency toward peribronchial infiltration.
3. The presence of a bronchial stenosis characterized by a partial or complete atelectasis of the affected portion of pulmonary tissue.
4. Retraction of the heart and mediastinal contents toward the affected side.
5. Upward retraction of the diaphragm on the affected side.

Fig. 4.—In right upper lobe a shadow the size of a child's fist, not sharply bordered and with finger-like offshoots; hilar infiltration on both sides. The roentgen diagnosis was tumor of the bronchus (?). Autopsy showed right superior bronchial carcinoma, second order.

Fig. 5.—In left hilar region a shadow, not sharply bordered, with infiltrating bands extending into the left lung; mediastinum displaced somewhat toward the left. The roentgen diagnosis was probable neoplasm of the bronchus of the left lung. Autopsy showed carcinoma of the left bronchus extending to the entrance of both the superior and the inferior bronchus.

6. In from 7.5 to 10 per cent, evidence of palsy of the phrenic nerve (more often left-sided), with paralysis of the corresponding side, and an accompanying paradoxical respiration.

7. Widening of the mediastinal shadow.

Figures 1 to 5, inclusive, demonstrate a few cases suggestive of a primary malignant process in the lung.

In cases of suspected malignancy, the difficulty at times lies in making a diagnosis that differentiates between a primary tumor of the lung and a mediastinal tumor. This difficulty is more apt to arise when

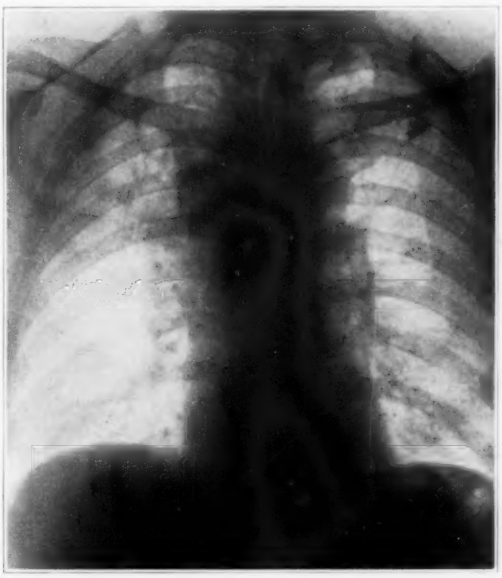

Fig. 6.—Marked mediastinal involvement and comparatively little infiltration of lung tissue. A barium sulphate meal demonstrates esophageal obstruction. The roentgen diagnosis was mediastinal tumor with esophageal obstruction. Autopsy showed carcinoma of the right main bronchus.

the primary tumor is located either in a main bronchus or in the first portion of a bronchus of an upper lobe (figs. 6 and 7). It may also arise in cases of tumor in a bronchus of the left inferior lobe because of the heart shadow covering the primarily affected area. The former group frequently metastasize very early to the mediastinum, showing a little hilar infiltration, which might readily be mistaken as secondary to a primary mediastinal tumor. Evidence of palsy of the phrenic nerve (in 7.5 per cent of this group) is strongly indicative of a malignant

process, as this condition rarely accompanies a tuberculous mediastinal involvement (figs. 3 and 7).

In the remaining group the roentgen diagnosis was necessarily secondary, showing either extensive pleural exudate (15 per cent), atelectasis (7.5 per cent), abscess cavity formation (5 per cent), a pneumonic infiltrate (2.5 per cent) or a suggestive bronchiectasis (2.5 per cent).

Roentgenography was also of value in confirming the clinical diagnosis of early metastases to the bone. These were more frequently found in the region of the chest although occasionally in the extremities. Emphysema was a frequent secondary observation.

Fig. 7.—Mediastinal tumor, more developed on the left side. There is some bandlike infiltration toward the apex of the left lung. The left side of the diaphragm is very high. The roentgen diagnosis was (1) mediastinal tumor with phrenic palsy (?) and (2) bronchial carcinoma (?). Autopsy showed carcinoma of the beginning of the bronchus of the left superior lobe.

The bronchoscope was employed in only 3 cases. In 2 the diagnosis of bronchial carcinoma was made, and in 1 of these cases was verified by biopsy. The third case was diagnosed as one of mediastinal tumor because, on examination, the bronchial mucosa appeared normal and the existing stenosis of the left main bronchus seemed the result of pressure from the outside. The primary growth in this case was situated in the second order bronchus of the left superior lobe.

Iodized oil was not injected in any of the 50 cases. The Wassermann reaction was positive in 2. These patients gave a long-standing history of syphilis. The sputum was examined in 70 per cent of the patients. In a few, the twenty-four hour specimen was observed and

measured. The quantity varied from a very small amount to 300 cc., the latter amount belonging to the group with large cavity or bronchiectatic formation. The amount varied according to the degree of bronchial stenosis present. In the stages of complete or almost complete bronchial occlusion there was little or no sputum. Increasing toxicity and a rise in temperature were accompanying factors. No mention was made of the sputum having a disagreeable odor. It varied from mucopurulent to purulent. Blood was noted in 16 per cent, tumor cells in 2 per cent and elastic fibers in 2 per cent; tubercle bacilli were absent in all cases.

Fig. 8.—Tumor infiltration at the beginning of the bronchus of the middle lobe and extending throughout the middle lobe. Several metastatic nodules are seen appearing on the surface of the right lower lobe. The lumen of the bronchus of the middle lobe is completely occluded.

A pleural puncture was performed in 18 per cent of the cases with the results shown in table 4. In 2 of the 4 cases reported as showing a hemorrhagic exudate, the first aspiration revealed a clear straw-colored fluid which later became hemorrhagic. The degree of anemia was slight during the early stages of the disease. As the metastatic involvement progressed, the anemia became more marked. A moderate leukocytosis with a corresponding increase in polymorphonuclear leukocytes was generally present. The principal clinical diagnoses are given in table 5.

The clinical course may be summarized as follows: Almost 80 per cent of the cases occurred in men, 50 per cent being between the ages of 50 and 60; 39 per cent of the parents died either from a cancer or of infection of the lung. Approximately 50 per cent of the patients gave a previous history of disease of the chest, a few histories being suggestive of recurrent attacks of bronchial stenosis. A study of occupation yielded little information. Perhaps 20 per cent of the patients could be said to have been subjected to more than the ordinary respiratory irritation aside from that caused by tobacco. Of interest is the fact that 44 per cent gave as their first symptom one that was not connected with the chest; 12 per cent went through the entire course of the illness

TABLE 4.—*Clinical Observations on Pleural Puncture*

	Number of Cases
Hemorrhagic	4
Purulent	3 } 9
Clear straw-colored	2
Tumor cells	1 (1 case ?)
Negative (tuberculin reaction)*	All
Specific gravity 1.018-1.022	
Culture: Hemolytic streptococcus	1
Pneumococci	1

* Negative for tubercle bacilli.

TABLE 5.—*Clinical Diagnosis in Fifty Cases*

No.		Per Cent
33	Primary pulmonary tumor (bronchial carcinoma in most cases)	66
7	Primary mediastinal tumor	14
3	Cerebral tumor (terminal pneumonia, 2)	6
2	Cardiac insufficiency; bronchitis; emphysema	4
1	Empyema	2
1	Sarcoma of uterus (metastasis to lung)	2
1	Carcinoma of ovary (metastasis to lung)	2
1	Chronic gangrenous pneumonia; cavitation	2
1	Exudative pleurisy; emphysema; bronchial pneumonia	2

without a pulmonary symptom. Blood-tinged sputum was observed in only 22 per cent, a fact that should warn one against a dismissal of the possibility of a malignant process in the absence of this finding. Hoarseness as a result of a recurrent nerve palsy was a rather common symptom and at times occurred early in the course of the illness. The left recurrent nerve is more apt to be involved than the right. Marked esophageal disturbance did not play a prominent rôle in this group, being noted in only 6 per cent.

Physical examination may reveal one or more of a large group of pathologic signs, and the best interpretation of these findings may be obtained by carefully repeated examinations. The gradual loss of weight, beginning cachexia and progressive anemia help one in diagnosing a malignant process. A marked degree of cachexia was more apt to be found in cases of advanced metastatic involvement. In those cases the suprarenals were frequently involved. Often, however, the

Fig. 9.—Whitish cancerous tissue at the entrance to the left main bronchus, extending along the left main bronchus and also infiltrating the surrounding lung tissue. More peripherally some of the lumina of dilated bronchi can be seen.

Fig. 10.—Following along the left main bronchus one observes the grayish-white tumor tissue at the entrance of the bronchus of the left superior lobe. Its lumen is almost entirely occluded, and the sectioned superior lobe, appearing very dark, is entirely atelectatic. On both sides at the beginning of the sectioned superior lobe bronchus, one sees a markedly enlarged, anthracotic lymph gland.

Fig. 11.—Tumor infiltration of the bronchial wall with polypoid growth into the lumen. A portion of bronchial cartilage is shown. The lower portion shows the chronically infiltrated lung tissue and a dilated bronchus with peribronchial leukocytic infiltration.

Fig. 12.—Normal appearing bronchi. The cut sections of the middle and lower lobes are entirely filled by diffuse grayish-white cancerous tissue.

patient did not show marked signs of inanition at autopsy, the skin, subcutaneous, and muscular tissues being well preserved.

The laboratory observations, singly or collectively, may prove of great value if examinations are carefully and thoroughly carried out. In a goodly percentage of cases one can diagnose a probable primary mediastinal or pulmonary tumor by means of roentgenograms. The differentiation between these two conditions as to which is primary is sometimes impossible to make. In other cases, because of a pleural exudate, atelectasis, large abscess formation, bronchiectasis, etc., the

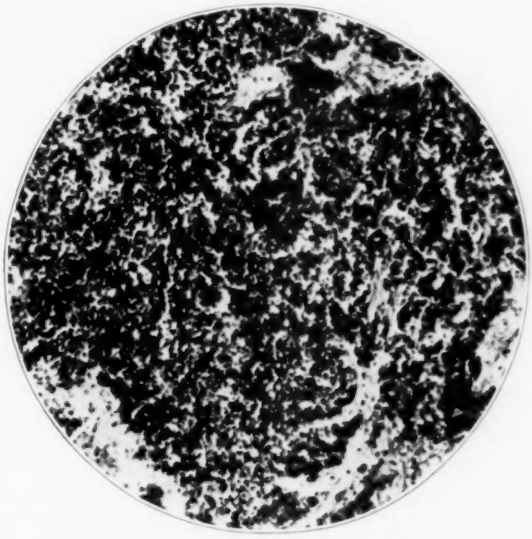

Fig. 13.—Small cell type of carcinoma showing the small cell proliferation almost solid in this view.

diagnosis may be secondary. A series of roentgenograms taken over a period of time may disclose the condition, whereas one plate may not. Roentgenography also provides a possibility of diagnosing early metastases to the bone.

Although not used in this series, iodized oil may be of considerable aid in the diagnosis, particularly in differentiating between a congenital and an acquired type of bronchiectasis with an existing bronchial stenosis. One can readily see the great value of bronchoscopy as a diagnostic aid, especially in the early course of the disease. In cases in which an operation is questionable, one can, with bronchoscopy, determine the extent of the tumor infiltration toward the main bronchi.

The sputum may be of great diagnostic value when carefully collected as a twenty-four hour specimen and not as an occasional one to be sent to the laboratory to be examined for tubercle bacilli. So also would be repeated aspirations in the event of pleural exudate, whereas an isolated aspiration might provide little information.

A marked drop in blood pressure, together with gastric symptoms and increasing cachexia, is suggestive of suprarenal involvement. This condition is not infrequently seen in the later stages of the disease.

I shall now consider the pathologic observations. The location of the primary growth is shown in table 6. A bronchial stenosis was present at the site of the primary growth in all of the cases of bronchial carcinoma. In most cases the entire wall of the bronchus was infiltrated with tumor tissue, and the mucosa was ulcerated in part or entirely

TABLE 6.—*Site of Primary Tumor in Fifty Cases*

	Right	Left	Total
Main bronchus	7	4	11
Bronchus of superior lobe	9	14	23
1st order	7	9	
2d order	2	3	
3d order	..	2	
Bronchus of middle lobe, 1st order	5	..	5
Bronchus of inferior lobe	3	6	9
1st order	2	4	
2d order	1		
3d order	..	2	
Alveolar cancer	..	..	2
Middle, inferior	1		
Superior	..	1	

at this point. In a few cases the tumor showed a marked tendency to spread along the bronchial wall for a considerable distance. In one case, for example, the primary growth started at the beginning of the bronchus of the middle lobe, and the tumor infiltration extended in the main bronchus and above the bifurcation as far as the upper border of the lower third of the tracheal wall. In a case of cancer of the right main bronchus the tumor was polypoid in appearance with a broad infiltrating base. This was the only case in which the infiltration was entirely confined to the wall of the bronchus with no pulmonary infiltration, and in which no metastases were found. In 52 per cent there was widening of the bronchial lumen peripheral to the stenosis. The picture presented by these dilated bronchi varied from a purulent bronchitis to a severe bronchiectasis. In the remaining cases the existing stenosis was not sufficient to cause more than a mild bronchitis in a few, while in others the bronchi were entirely destroyed by a tumor or abscess formation. In another small group the peripheral bronchi remained unchanged because of collapse of the lobe due to the presence of a pleural exudate. In 1 case, two primary growths were

found, one in the bronchus of the left superior lobe, second order, and the other in the bronchus of the right inferior lobe, first order.

The changes in the lung are shown in table 7 and in figures 8, 9, 10 and 11. Figure 11 shows typical changes in the lung in the presence of a malignant process. The small cell tumor invasion with infiltration of the bronchial wall and lumen, the existing bronchiectasis with peribronchial leukocytic infiltration and the chronic fibrotic infiltration of the remaining pulmonary tissue are all clearly brought out by this slide.

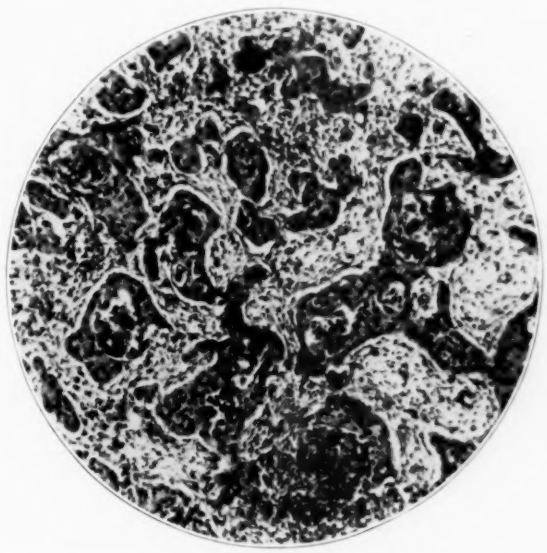

Fig. 14.—Squamous cell type of carcinoma showing numerous horn pearls.

In the 2 cases of alveolar carcinoma both lungs were infiltrated by tumor tissue, the primary side being almost entirely involved (fig. 12).

The pleural observations are given in table 8 and the metastatic observations in table 9. Table 9 shows the high percentage of mediastinal involvement by the lymphatic route. Of special interest also is the high percentage of metastases to the bone and brain, mainly by the blood route. In 9 cases there was bilateral involvement of the suprarenal glands, and in 8 cases, unilateral involvement. These conditions together represented 34 per cent. The unilateral cases were equally divided. Practically the same division held true in the case of the kidneys, 6 cases showing bilateral involvement, and 5 cases, unilateral. Of the unilateral cases, 3 were left-sided.

The pathologic diagnosis showed 48 cases of primary bronchial carcinoma, 1 of which revealed two primary tumors, and 2 cases, alveolar carcinoma. The types of carcinoma found were: (1) small cell, 68 per cent (fig. 13); (2) squamous cell (with or without horn

TABLE 7.—*Observations on the Lung in Forty-Eight Cases of Bronchial Carcinoma*

	A_1	A_2	B_1	B_2	B_3
Tumor infiltrate	10	..	37	7	..
Metastases	2	..	6	8	3
Pneumonia: Bronchial	2	1	1	3	1
Pneumonia: Indurative	1 (6)	..	8 (11)	2	..
Pneumonia: Gangrenous	3	..	2	..	..
Atelectases: Pleural exudate	2	..	4 (15)	6	..
Atelectases: No pleural exudate	2 (4)	..	11	..	..
Large abscess	1	..	3	..	..
Emphysema	1	1	..	5	10

A_1: Cancer of the stem bronchus (affected lung), 11 cases
A_2: Opposite lung
B_1: Cancer of bronchi within a lobe (affected lobe), 37 cases
B_2: Adjacent lobe
B_3: Opposite lung

TABLE 8.—*Pleural Observations at Autopsy*

	Affected Side, per Cent	Free Side, per Cent
Adhesions	78	30
Tumor infiltration	16	..
Metastases	20	8
Exudate	52	12
Clear straw-colored	24	10
Hemorrhagic	10	..
Purulent	18	2
Fibrinous pleurisy	6	2

TABLE 9.—*Metastases in Fifty Cases*

	Per Cent		Per Cent
Mediastinum	78	Thyroid	8
Bone	38	Skin; spleen	4
Liver; suprarenals	34	Stomach; bladder	
Lung	28	Omentum; muscle	
Kidneys	22	Bronchi; intestines	2
Cervical glands	20	Seminal vesicles	
Brain; pleura	12	Ureter; uterus	
Pericardium		Peritoneal glands	
Myocardium	10	Superior vena cava	
Peritoneum		Submaxillary glands	
Retroperitoneal glands		Spinal cord	
Pancreas			

pearls), 20 per cent (figs. 14 and 15); (3) adenocarcinoma, 8 per cent (fig. 16), and (4) alveolar carcinoma, 4 per cent (fig. 17).

A summary of the pathologic observations is as follows: There is an equal tendency to tumor formation in either lung; 46 per cent occurred in the upper lobes as compared with 28 per cent in the middle and lower lobes; 76 per cent were found in the right or left main bronchi or in the first portion of the bronchi of the main lobe. The

primary growths situated in the main bronchi metastasize to the mediastinal lymph nodes in a very early stage and are a little slower to metastasize by the blood stream. A varying degree of bronchial stenosis is always present in cases of bronchial carcinoma, and is often accompanied by a peripheral bronchiectasis or, in a few cases, peripheral abscess formation. Atelectasis as a result of bronchial stenosis, tumor infiltration or pleural exudate of the involved or adjacent lung is a frequent finding. Various pneumonic changes are often present, chronic induration being the more frequent type in the affected lobe. Emphysema may be found in the adjacent lobe or in the opposite lung.

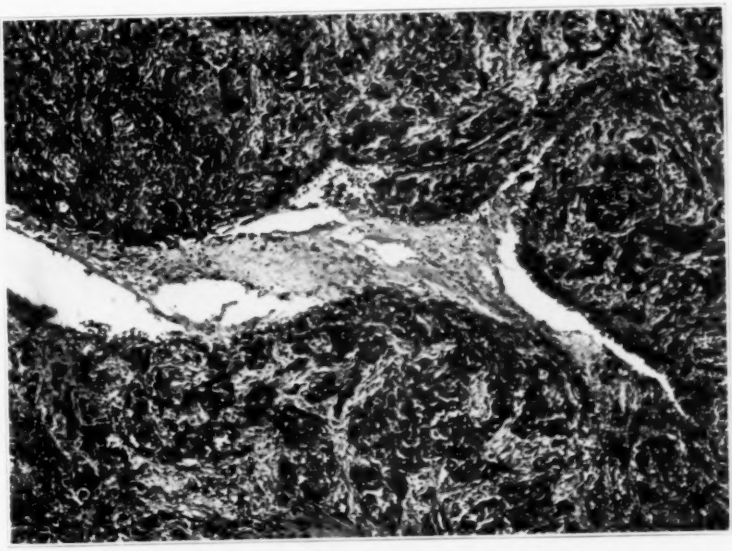

Fig. 15.—Squamous cell type of carcinoma without horn pearl formation. The bronchial lumen is almost closed. A portion of bronchial cartilage is seen in the lower border.

In a few cases enlarged, chronically inflamed lymph glands were found around the hilar region as evidence of a long-standing or previous inflammatory condition. Pleural adhesions were commonly present, and almost 80 per cent of the patients had adhesions on the primary side, these being the result of an old inflammatory pleurisy, inflammatory changes during the present illness or tumor infiltration or metastasis. A pleural exudate was present in 52 per cent, while a hemorrhagic exudate was present in only 10 per cent. Tumor infiltration and metastasis to the pleura occurred in 36 per cent on the primary

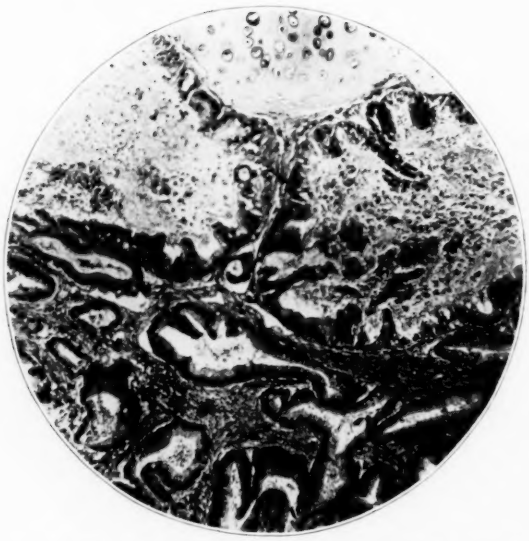

Fig. 16. Adenocarcinoma; the upper portion is bronchial cartilage and the remainder glandular proliferation with considerable mucus in the lumen.

Fig. 17.—Alveolar type of carcinoma; a special stain has been used to bring out the alveolar structure. Enlargement and proliferation of the alveolar cells are readily seen.

side. This shows the relative infrequency of a hemorrhagic exudate even in the presence of invasion by a tumor.

Pulmonary carcinomas are in most cases rather rapidly infiltrating tumors, tending to metastasize early by both the lymphatic and blood routes. Mediastinal nodes were involved in almost 80 per cent of the cases. These tumors show a marked tendency toward metastases to the bone, cerebrum, liver and suprarenals. In 3 cases the cerebral metastases were the only ones found. In 1 case the tumor was confined to the bronchus with no pulmonary or mediastinal involvement. In 3 cases the tumor was confined to the bronchus and lungs, and in 1 case the involvement was entirely confined to the bronchus and its corresponding lobe.

In the present series of cases, carcinoma was the only type of malignant growth found. Bronchial carcinoma was found in 96 per cent and alveolar carcinoma in 4 per cent. Of the bronchial carcinomas the small cell type predominated, occurring in 68 per cent.

CONCLUSIONS

Primary carcinoma of the lung is a comparatively frequent finding in the larger pathologic institutes. These tumors, in consideration of the time element from the first symptom to death, run a rapidly fatal course. The few patients with early suggestive pulmonary symptoms should be examined with great thoroughness, using all the available measures at one's disposal, to help in establishing an early diagnosis. By so doing, one may increase the percentage of diagnoses made while the tumor is confined to one lobe. In such a group lobectomy is indicated as a possible measure.

For the large percentage of cases in which operative intervention is not indicated, roentgen or radium therapy may considerably retard the growth and spread of the cancer and also help to alleviate disturbing symptoms caused by metastases.

Carcinoma of the lung should be classified with that of the mamma, thyroid, prostate and suprarenals as showing a very early tendency toward metastasis to bone.

STREPTOCOCCI IN THE BLOOD IN RHEUMATIC FEVER, RHEUMATOID ARTHRITIS AND OTHER DISEASES

BASED ON A STUDY OF 5,233 CONSECUTIVE BLOOD CULTURES

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A review of the literature dealing with the etiology of rheumatic fever shows clearly that much of the controversy in this important field is due to the paucity of adequate controls. It is a curious but undeniable fact that though bacteriologic investigations on this disease date back more than forty-five years, few of the numerous reports published are critical or well controlled. In order to establish a suitable background for the work to be reported in this paper, it may be well to mention briefly a number of the methods by which this problem has been attacked and to point out the doubtful justification in many instances for the conclusions drawn from the data obtained:

1. The description of organisms found post mortem and their acceptance as the etiologic agent of rheumatic fever. This error dates back to the work of Birch-Hirschfeld,[1] and was repeated by numerous investigators. In a study of the post-mortem bacteriologic changes in patients dying from diseases other than rheumatic fever, Epstein and Kugel [2] showed that streptococci can be recovered at autopsy in 40 per cent of cases from normal heart valves, in 47 per cent from the myocardium and in 79 per cent from the blood stream.

2. The alleged finding of specific streptococci in the throats of patients with rheumatic fever. Irvine-Jones [3] showed that these organisms could not be distinguished culturally or immunologically from those found in normal throats. Hitchcock [4] found streptococci almost as frequently in the throats of nonrheumatic as in those of rheumatic patients.

3. The significance given to the finding of minimal numbers of streptococci in the joints or subcutaneous nodules in cases of rheumatic fever. Shands [5] has recently reported the finding of streptococci in 2 of 10 Charcot joints and in 1

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1. Birch-Hirschfeld: Wiesbaden Medical Congress, 1888; quoted by Thomson, D., and Thomson, R.: Annals of the Pickett-Thomson Research Laboratory **4**:1 (Nov., pt. 1) 1928.

2. Epstein, E. Z., and Kugel, M. A.: J. Infect. Dis. **44**:327, 1929.

3. Irvine-Jones, E. I. M.: Skin Sensitivity of Rheumatic Subjects to Streptococcus Filtrates, Arch. Int. Med. **42**:784 (Nov.) 1928.

4. Hitchcock, C. H.: J. Exper. Med. **42**:377, 1925.

5. Shands, A. R.: South. M. J. **23**:818, 1930.

gonorrheal arthritic joint (with gonococci). We have had similar experience with the latter condition. Menkin[6] has given experimental proof of the secondary localization of organisms in an inflamed site.

4. The serologic behavior of streptococci. Few efforts have been made to classify serologically the streptococci obtained in cases of rheumatic fever and rheumatoid arthritis. In most instances agglutinin absorption was not attempted. Recently, however, by the use of agglutination as well as agglutinin absorption methods, Cecil, Nicholls and Stainsby[7] were able to group the Streptococcus alpha organisms obtained from the blood and joints of patients with rheumatic fever into 3 types and a fourth heterogeneous group. It remains to be determined whether secondary invaders cannot be similarly grouped.

5. The results obtained from the injection of vaccines and serum. These results are still used as arguments to support the contention that a given organism is the etiologic agent of rheumatic fever. The difficulty of differentiating specific from nonspecific effects, together with other obvious objections to the acceptance of this form of evidence, is too well known to require discussion.

6. The results of skin tests. Following Birkhaug's[8] demonstration that persons who have suffered from rheumatic fever are more susceptible to intracutaneous injections of toxic filtrates from Streptococcus gamma than are other groups of persons, Swift, Derick and Hitchcock[9] showed the same to be true for Streptococcus alpha, as well as nucleoproteins from various types of streptococci. These authors also showed that patients suffering from other diseases displayed a similar skin sensitivity to these products.

7. The confusion of bacterial endocarditis with verrucous endocarditis of the rheumatic type, or the tacit acceptance that one is a modification of the other. This confusion has led to unjustified conclusions of experimental results.

8. The experimental production of pathologic lesions (endocarditis, pericarditis, arthritis and myocarditis) in animals, with the assumption that this is evidence of the specificity of an organism with relation to the etiology of rheumatic fever. Cole,[10] Harris[11] and Horder[12] were the first to correct this error by showing that a variety of streptococci may produce these lesions when injected into animals. Recently, similar efforts have been made with regard to subcutaneous nodules.

9. The acceptance of certain forms of endocarditis and myocarditis produced in animals (particularly in rabbits) as the equivalent of rheumatic lesions in the human being. This point has been critically examined and discussed by Thalhimer and Rothschild,[13] Cecil,[14] Swift[15] and Gross, Loewe and Eliasoph,[16] who showed that the lesions thus far produced experimentally cannot be so considered.

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6. Menkin, V.: J. Exper. Med. **53**:647, 1931.

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9. Swift, H. F.; Derick, C. L., and Hitchcock, C. H.: Tr. A. Am. Physicians **43**:192, 1928.

10. Cole, R. I.: J. Infect. Dis. **1**:714, 1904.

11. Harris, N.: Tr. Chicago Path. Soc. **6**:303, 1905.

12. Horder, T. J.: Thirty-Sixth Annual Report of the Local Government Board, Report of the Medical Officer, 1906, p. 279; Quart. J. Med. **2**:289, 1908.

13. Thalhimer, W., and Rothschild, M. A.: J. Exper. Med. **19**:429, 1914.

14. Cecil, R. L.: J. Exper. Med. **24**:739, 1916.

15. Swift, H. F.: Am. J. M. Sc. **170**:631, 1925.

16. Gross, Louis; Loewe, Leo; and Eliasoph, B. J.: J. Exper. Med. **50**:41, 1929.

10. Failure to recognize spontaneously occurring lesions in laboratory animals. Miller [17] was able to show that his control rabbits and guinea-pigs possessed myocardial lesions that he could not differentiate from those that he had attempted to reproduce experimentally.

11. The significance attached to the finding during life of positive blood cultures, particularly of streptococci. It is with this last point that this article is concerned. Several excellent critical reports have been published on this aspect of the problem of rheumatic fever, among which may be mentioned those by Cole,[10] Libman,[18] Swift and Kinsella [19] and Jordan.[20] Many discrepancies exist as to the frequency with which various authors obtained positive blood cultures (streptococci) from cases of rheumatic fever, the optimum method to be used for this purpose and the type of streptococci recovered. On the latter point, it may be mentioned that Streptococcus alpha, beta and gamma have been found.

On the question of the percentage of positive blood cultures, figures vary from completely negative findings to such successful reports as those of Clawson,[21] who isolated streptococci "in a relatively high percentage of cases," and those of Cecil, Nicholls and Stainsby,[7] who obtained positive blood cultures in 26 of 31 cases (83.9 per cent) in their series of 1929. The latter investigators attributed their successes to the special technic used. The value of the special technic has been questioned by Nye and Waxelbaum [22] and by Dawson, Olmstead and Boots,[23] who were unable to confirm the results obtained in cases of rheumatoid arthritis. Incidentally, the criticisms that have thus far been made generally apply equally well to the reports on the bacterial etiology of rheumatoid arthritis.

In examining the reports of those who obtained a relatively high incidence of streptococcemia in rheumatic fever and because of this are inclined to accept these organisms as the causative agent of the disease, it becomes apparent that in none of these studies were there employed as controls groups of diseases selected from as large a material as that from which the cases of rheumatic fever were drawn.

The records in the Mount Sinai Hospital for the last four and a half years (ending Dec. 30, 1930) show that blood cultures were taken in 188 cases of acute rheumatic fever with polyarthritis, in 126 cases of chronic rheumatic cardiovalvular disease with recurrences and in 49 cases of rheumatoid arthritis (for an explanation of the terms, see section on "Definitions," p. 1082). A study of the incidence of strepto-

17. Miller, C. P.: J. Exper. Med. **40**:525 and 543, 1924.

18. Libman, E.: Bull. Johns Hopkins Hosp. **17**:215, 1906; Characterization of Various Forms of Endocarditis, J. A. M. A. **80**:813 (March 24) 1923; New York Academy of Medicine Lectures on Medicine and Surgery, New York, Paul B. Hoeber, Inc., 1927, vol. 69.

19. Swift, H. F., and Kinsella, R. A.: Bacteriologic Studies in Acute Rheumatic Fever, Arch. Int. Med. **19**:381 (March) 1917.

20. Jordan, E. P.: The Microbic Etiology of Rheumatic Fever and Arthritis, Arch. Path. **10**:79 (July) 1930.

21. Clawson, B. J.: J. Infect. Dis. **36**:444, 1925.

22. Nye, R. N., and Waxelbaum, E. A.: J. Exper. Med. **52**:885, 1930.

23. Dawson, M. H.; Olmstead, M., and Boots, R. H.: Proc. Soc. Exper. Biol. & Med. **28**:419, 1931.

coccemia in these diseases can be of significance only if compared with other selected diseases or disease groups drawn from the total blood culture material from which the aforementioned groups were taken—in effect, from 5,233 cases. An investigation of this point was undertaken and forms the basis of this report. Furthermore, since it is the main purpose of this work to serve as an adequate control of the bacteriologic findings in the blood of patients suffering from rheumatic fever and rheumatoid arthritis and since alpha and gamma streptococci are the organisms most frequently found in these diseases, we chose our control groups with the following criteria in mind:

1. The diseases should not be obviously caused by a nonhemolytic streptococcus.

2. They should not be obviously associated with a massive blood invasion with nonhemolytic streptococci, such as occurs in subacute bacterial endocarditis.

3. The percentage incidence of the nonhemolytic streptococcemia should be within the same range as that found in rheumatic fever and rheumatoid arthritis.

MATERIAL

Our material consists of 5,233 consecutive blood cultures taken, during the latter half of 1926 and during the years 1927, 1928, 1929 and 1930, from 3,869 patients in whom the possibility of a blood invasion was considered. Positive bacteriologic findings were obtained in 762 subjects. During this entire period there was little change in the full time bacteriologic staff, the entire work having been carried on under the supervision of Dr. Gregory Shwartzman. After the elimination from the control groups of the diseases that did not fulfil the requirements mentioned, the disease groups on which special emphasis will be laid may be tabulated as follows:

Rheumatic and Rheumatoid Group	Cases
I. Acute rheumatic fever with polyarthritis*	188
II. Chronic rheumatic cardiovascular disease*	126
III. Rheumatoid arthritis*	49
Control Group	
IV. Aplastic anemia	13
V. Pernicious anemia	11
VI. Leukemia	29
VII. Colitis*	41
VIII. Meningococcus meningitis	54
IX. Pyelitis and pyelonephritis	72

* For an explanation of the terms, see "Definitions," p. 1082.

DEFINITIONS

The accepted diagnostic criteria of active rheumatic infection, including tachycardia, fever, sedimentation time, leukocytosis, electrocardiographic changes, etc., were used in selection of the rheumatic cases. In order to determine whether there was any difference, so far as the incidence of streptococcemia was concerned, between the very active, acute form with polyarthritis and the milder form with recurrent attacks in which the mechanical symptoms predominate (i. e., due to the valvular defects), the cases were divided into two groups: acute rheumatic fever with polyarthritis and chronic rheumatic cardiovalvular disease.

Acute Rheumatic Fever with Polyarthritis.—This group comprises typical cases in which polyarthritis is the predominant symptom. Only cases in which there was fever, leukocytosis or both are included. One case of chorea is also included.

Chronic Rheumatic Cardiovalvular Disease.—As stated, this group includes cases in which the valvular defects on a rheumatic basis predominate, with recent reinfection, but without polyarthritis. Cases of atherosclerotic heart disease complicated by febrile conditions were obviously excluded from this group.

Rheumatoid Arthritis.—This comprises a group of patients suffering from acute, subacute or chronic so-called infectious monarticular or polyarticular arthritis of nonrheumatic origin, and corresponds to the "rheumatoid arthritis" group under the classification of the British Ministry of Health and adopted by the International League for the Control of Rheumatism. Cases of gonorrheal origin were excluded. All of the patients, with rare exceptions, had fever, leukocytosis or both. Some had involvement of single joints; others, of multiple joints.

Colitis.—Under this term are included cases of acute and chronic ulcerative colitis. Cases of amebic and tuberculous colitis are excluded.

Streptococcemia.—We use this term to denote the presence of streptococci in the blood during life, giving it the same generic meaning as "bacteremia" as defined by Libman.[18] The term in no way indicates whether the invasion is transient or an essential part of the disease process.

Nonhemolytic Streptococci.—The Brown[24] classification of streptococci is used in this report. In the older literature no sharp differentiation was made between Streptococcus alpha and gamma. Furthermore, it is particularly these two types that occur most frequently in cases of rheumatic fever and rheumatoid arthritis, and they are the basis of

24. Brown, J. H.: Monogr. Rockefeller Inst. M. Research, 1919, no. 9.

most of the comment. For these reasons we shall refer to the organisms collectively as "nonhemolytic streptococci" in the sense used by Libman.[18]

U Cocci.—In a number of cases a gram-positive coccus was obtained on blood culture, which, however, failed to grow on aerobic subcultures, so that it could not be identified. The failure to grow may have been due to two reasons: prompt autolysis in the medium or unsuitable aerobic conditions (if they were anaerobes). In some instances, however, growth did not take place even under strict anaerobiosis. These unidentified organisms will be referred to as U cocci, and will be given consideration so as to present an unbiased statistical picture.

TECHNIC OF THE BLOOD CULTURE

The antecubital area is sterilized by tincture of iodine, which is removed with alcohol in from three to five minutes. At least 23 cc. of blood is withdrawn from the median basilic vein; when special cultural methods are employed, 40 cc. is withdrawn. The various mediums are inoculated immediately at the bedside, and plates are poured.

In taking routine blood cultures, the following equipment is used: glass Luer syringes, of 20 cc. capacity; needles, sterilized by means of dry heat in a special copper container at 185 C. for an hour and a half; 4 sterile petri dishes; 2 test tubes, each containing 1 cc. of sterile ascitic fluid; 2 sterile, empty test tubes; 1 tube of plain agar; 1 flask of plain broth; 1 flask of 2 per cent dextrose broth, and 1 flask of tomato dextrose peptone broth. The preparation of the special mediums will be described in the next section. The last 6 mediums mentioned constitute our "*Routine*" mediums.

The agar tubes are previously melted and kept at 50 C. The patient's blood is then drawn and distributed as follows: 5 cc. to each flask; 2 cc. each to the plain agar, dextrose agar and liver hormone agar tubes. Before pouring the plates, the agar and blood are mixed by pouring back and forth into sterile tubes under strict sterile precautions. One tube of dextrose agar and another of liver hormone agar are enriched with ascitic fluid before the plates are poured. One tube of ascitic fluid mixed with 5 cc. of dextrose broth serves as a control for the sterility of the ascitic fluid. Likewise, the individual mediums are controlled for absolute sterility. Within half an hour, all the mediums are incubated at 37.5 C. The plates are examined daily, and by means of a capillary pipet subcultures are made daily from the 3 flasks on dextrose broth and dextrose ascitic agar. This procedure is repeated for four days if the cultures are negative. All gram-positive, chain-forming diplococci that do not show definite zones of complete hemolysis around the colonies on the blood plates are typed for pneumococcus and tested for bile solubility.

CULTURE METHODS

The special cultural methods employed are the anaerobic, the special aerobic and the method of Cecil, Nicholls and Stainsby. The following anaerobic culture mediums were used: the Smith-Noguchi rabbit kidney ascitic fluid, the Rosenow calf brain and cooked liver. The formulas for these mediums will be given. Two cubic centimeters of the patient's blood is added to each of the mediums in tubes, which are sealed with melted petrolatum. After incubation at 37.5 C. for three days, the

tubes are opened; the films are stained, and the inoculum is transferred from each tube to cooked liver. All the tubes are then sealed and incubated for three days more. They are then opened and examined for growth. If negative, they are sealed and incubated for two weeks more, when a final examination and report are made.

Special Aerobic Method.—This method was carried out as follows: from 10 to 12 cc. of the patient's whole blood was inoculated into a 500 cc. Erlenmeyer flask containing 100 cc. of 0.4 per cent dextrose broth (p_H 7.4). Daily subcultures were made for a week. The features of the method are the large amount of blood used and the large surface of medium exposed to air.

Cecil Procedure.—This procedure was carried out in detail as originally described. Twenty cubic centimeters or more of blood is taken from a vein of the arm. The blood is divided between two centrifuge tubes, allowed to clot and stored in the ice chest over night. The following morning the clots are loosened with a glass rod, and the tubes are placed in the centrifuge. After centrifugation, the serum is carefully removed with a pipet, and the clots are broken up with glass tubes one-fourth of an inch (0.64 cm.) in diameter, drawn up in the tubes and transferred to two 3 ounce (11.25 cc.) bottles, each containing 50 cc. of beef heart infusion broth. The bottles are covered with paper caps and incubated at 37 C. for one month. During this period the bottles are opened at five day intervals and subcultures are made on both blood agar-poured plates and blood broth tubes, 0.1 cc. of the original broth culture being used in each case. If no growth is found at the end of a month, the original contents of the broth bottles are centrifugated and the sediment is cultured in fresh blood broth. Subcultures are made from the sediment on blood agar plates several days later, and if no organisms are found, the cultures are considered negative. Parallel control cultures are made of the rabbit's blood for a period corresponding to that during which the patient's blood is studied. The rabbit's blood is transferred to dextrose broth every five days, and films of the sediment are stained.

PREPARATION OF MEDIUMS

Plain Broth.—To 500 Gm. of chopped meat (beef or veal) is added 1,000 cc. of tap water. The mixture is brought to the boiling point over an open flame and cooked slowly for fifteen minutes; it is then filtered through absorbent cotton and readjusted to the amount of 1,000 cc. To this infusion is added 10 Gm. of Witte's peptone and 4 Gm. of sodium phosphate. The p_H is adjusted to 7.8. The mixture is autoclaved for twenty minutes at 15 pounds of pressure, and the reaction is readjusted to a final p_H of 7.4 or 7.6.

Liver Hormone Broth and Agar.—To 500 Gm. of chopped veal or beef liver freed from fat are added 1,000 cc. of water, 10 Gm. of peptone, 4 Gm. of anhydrous sodium phosphate, 10 Gm. of dextrose, the beaten whites of 2 eggs and 20 Gm. of agar (if used for agar). All the ingredients are placed in the same receptacle and heated over a free flame up to 70 C., when the meat turns brown. Twenty-five cubic centimeters of sodium hydroxide is then added. Sterilization is carried out in the Arnold sterilizer for two hours. At the end of this time a firm clot is formed and the broth or agar can be decanted or siphoned off. The preparation is not filtered at any stage. The reaction is adjusted to p_H 7.6. The medium is autoclaved in flasks for twenty minutes at 15 pounds of pressure. After transfer to tubes it is again autoclaved for fifteen minutes and 15 pounds of pressure.

Tomato-Dextrose-Peptone Broth (Shwartzman).—Tomatoes are washed in warm water and gently dried with a towel. Small pieces are cut and boiled for fifteen minutes over an open flame. The preparation is filtered first through gauze and then through absorbent cotton. The extract is stored in the ice chest over night. The next day it is filtered by means of suction through several layers of paper in a Buchner funnel. After this the fluid is clear enough to be filtered through Berkefeld filters, candle V being used first and then candle N. No further sterilization is necessary. The fluid is stored in the ice chest until needed. Before use the reaction is adjusted by means of sterile sodium hydroxide, which is added to the extract until the color changes to a light brown. This indicates a p_H of about 7.6. To 90 cc. of 2 per cent peptone and 1 per cent dextrose broth is added 10 cc. of sterile tomato extract. The mixture is then sterilized in the Arnold sterilizer for ten minutes. The medium thus prepared rarely proves to be contaminated.

Cooked Liver.—To 1,000 cc. of 1 per cent dextrose broth is added 1 pound (453.6 Gm.) of beef liver. The mixture is boiled over an open flame for fifteen minutes. The reaction is adjusted to p_H 7.6. The liver is cut into small cubes and placed in tall tubes used for the Smith-Noguchi medium and autoclaved for twenty minutes at 15 pounds of pressure.

Rosenow Calf-Brain Medium.—A small piece of white marble is introduced into a tube, then a cube of raw calf brain and 10 cc. of plain broth. The p_H is adjusted to 7.4. The mixture is autoclaved for thirty minutes at fifteen pounds of pressure.

Cecil, Nichols and Stainsby's Beef Heart Infusion Broth.—This medium was carefully prepared and adjusted as described in the original work. The blood agar plates were made as follows: eight cubic centimeters of agar (1.5 per cent beef heart infusion) is melted and cooled to 50 C. To this are added 0.5 cc. of whole rabbit blood and 0.1 cc. of the original broth culture, and the plate is poured.

BACTERIOLOGIC RESULTS OF BLOOD CULTURES

I. *Acute Rheumatic Fever with Polyarthritis.*—One hundred and eighty-eight cases are included in this group. While cultures were taken in many cases in which salicylates were not administered, no especial control of this factor was made. With a single exception, all the patients were febrile or had leukocytosis at the time the blood was examined.

Negative Results: In this series, 168 cases proved sterile. Of these cases, 13 were fatal. Twenty-three cases of this negative group were cultured on two occasions, 4 on three occasions, 1 on five occasions, and 1 nine times. One hundred and fifty-eight of these cases were studied with routine methods only. In addition to the routine mediums, however, 77 cases were studied by the special aerobic method, 10 by the Cecil and 65 with the aid of the anaerobic Smith-Noguchi, Rosenow, or cooked liver mediums.

Positive Results: Positive bacteriologic findings were obtained in 20 cases. In 5 cases the cultures were repeated. Gram-positive cocci were obtained in 2 of the repeated cultures. There was only 1 fatal case in this series. In 3 of 20 instances in which gram-positive cocci were obtained it was impossible to obtain growth on subculture. Of the 17 that grew on subculture, 1 was Streptococcus beta, 1 pneumococcus type II, 4 Streptococcus alpha and 11 Streptococcus gamma (8 per cent nonhemolytic streptococci). B. coli was obtained in 1 of the cases in which the gram-positive organism did not grow on subculture.

In 10 of the positive cases, routine mediums only were employed. In the other 10, special mediums were used in addition. Twelve cultures were made. In only 1 of the latter group did an organism appear (Streptococcus alpha) on the special mediums alone (special aerobic). On the other hand, whereas organisms grew in 9 of these 12 cultures in the routine mediums, growth was obtained in only 4 in the special mediums.

Considering the group as a whole, of the 178 cases studied by the routine methods, positive results were obtained in 19 (11 per cent). Of the 86 cases studied by the special aerobic method, 3 were positive (3.5 per cent). The organisms were all Streptococcus alpha. Of the 11 cases studied by the Cecil method, none was positive. The 67 anaerobic cultures were all negative. The question of the relative value of different mediums will be discussed later.

II. *Chronic Rheumatic Cardiovalvular Disease.*—This group comprises 126 cases, in practically all of which there was fever or leukocytosis, or both.

Negative Results: The blood cultures in 119 cases of the series yielded negative results. Fifteen of the cases were fatal. In 5 of the negative cases the blood was cultured twice; in 2, 3 times, and in 1,

4 times. Thirty-six cases were studied by the special aerobic technic. None of these cases was studied by the Cecil method. Forty-six cases were studied anaerobically with the Smith-Noguchi, Rosenow and cooked liver mediums.

Positive Results: Seven of the cases in this group yielded gram-positive cocci on blood culture. In a single case the organism failed to grow on subculture. In addition to the unidentified coccus an unidentified bacillus that failed to grow on subculture was obtained on anaerobic mediums. Of the remaining 6 cases, 3 showed Streptococcus alpha and 3 Streptococcus gamma (5 per cent nonhemolytic streptococci). Three of these cases were fatal. Two of the 7 cases were studied by the special aerobic technic, none by the Cecil method and 4 by anaerobic methods.

In the 5 cases in which routine as well as special mediums were used, 7 cultures were taken. Organisms were obtained in the routine mediums in 5 cultures and in the special mediums in 3. In 1 of these, growth was obtained in the special aerobic flask only—not in the routine mediums.

Considering the group as a whole, of the 125 cases studied by the routine methods, positive results were obtained in 5 (4 per cent nonhemolytic streptococci). Of the 38 cases studied by the special aerobic method, 2 were positive, 1 yielded Streptococcus alpha and 1 streptococcus gamma (5 per cent nonhemolytic streptococci). The Cecil method was not used in this group. The 50 anaerobic cultures were negative.

III. *Rheumatoid Arthritis.*—Forty-eight cases of acute, subacute and chronic infectious arthritis were studied. There were no fatalities in this series.

Negative Results: In 44 cases the blood cultures were negative. In 9 of these, the cultures were repeated. Eighteen cases were studied by the special aerobic technic, in 1 case 3 times and in another twice. In 5 cases the cultures were taken according to the Cecil procedure, and in 7 cases, anaerobically.

Positive Results: Four cases yielded gram-positive cocci in the blood cultures. In 2 of these, the organism failed to grow on subculture. On repetition in one of the cases, a hemolytic streptococcus and Staphylococcus albus were obtained. In the remaining 2 cases, Streptococcus gamma grew (4 per cent nonhemolytic streptococci).

In 4 positive cases, 8 cultures were taken. In all of these, routine mediums were used. In addition, special mediums were used in 6 of the cultures. Organisms grew in the routine mediums in 3 cultures and in the special mediums in 2. In a single case growth was obtained on the special mediums only (special aerobic and Rosenow's).

Considering the group as a whole, of the 44 cases studied by routine methods, positive results were obtained in 4 (9 per cent). Two of these showed nonhemolytic streptococci (4.5 per cent). Of the 21 cases

studied by the special aerobic method, 1 was positive and showed Streptococcus gamma (5 per cent). Five Cecil cultures were negative. Ten cases studied with anaerobic methods gave 2 positive results: 1 Streptococcus gamma (10 per cent), and 1 an unidentified gram-positive coccus that failed to grow on subculture.

Of the 3,869 cases in which blood cultures were taken, 363 comprise the 3 groups just considered and 144 were cases of subacute bacterial endocarditis in which a streptococcemia is to be expected in a large proportion of cases. If we eliminate the total of these 2, 3,362 cases are left, in which nonhemolytic streptococci and U cocci were found in 51 (1.5 per cent) and nonhemolytic streptococci in 43 (1.3 per cent).

The accompanying table lists all cases in which nonhemolytic streptococci and U cocci were found in the blood of the control series, and also data on the mediums used, the temperature of the patient at the time the cultures were taken, the white blood cell count and the final diagnosis. Whereas no indication is given in the table of the total number of cases making up the different diseases studied, it may be said at once that with the exception of the conditions listed as "control groups" the incidence of nonhemolytic streptococcemia in any given group was under 1.5 per cent. Routine mediums were employed in all the positive cases. In addition, in 17 cases the special aerobic method was added; in 2 cases, the Cecil method, and in 12 cases, anaerobic method.

IV. *Aplastic Anemia.*—There were 13 cases in this group, with 2 positive results (15.5 per cent); in 1, Streptococcus alpha; in the other, Streptococcus gamma (see table, cases 1 and 2). A single anaerobic culture was employed, with negative results. The positive results were obtained on routine mediums. Both cases terminated fatally.

V. *Pernicious Anemia.*—There were 11 cases in this group, with 1 positive result (Streptococcus alpha), which was obtained in routine mediums (9 per cent). This case was fatal (see table, case 5).

VI. *Leukemia.*—There were 29 cases in this group. In 2, Streptococcus gamma was obtained in the routine mediums (7 per cent). The cases were fatal (see table, cases 3 and 4).

VII. *Colitis.*—There were 41 cases in this group, with 4 positive results (10 per cent) (see table, cases 7 to 10). Routine mediums only were used in the 5 cultures taken. Streptococcus gamma (identified as Enterococcus by esculin fermentation test, etc.) was obtained in 1 case, and in another Streptococcus alpha was obtained on solid mediums (5 per cent nonhemolytic streptococci). In 2 cases U cocci were found, and in 1, Staphylococcus albus. The latter case was the only one in which the patient survived.

Cases of Nonrheumatic-Rheumatoid Disease with Nonhemolytic Streptococci or

Case	Blood Culture No.	Mediums	Temperature, F.	White Blood Cells	Bacteriologic Findings	Clinical Result and Diagnosis
1	13714	R.	103.0	1,200	SG-2; tomato extract	Died; aplastic anemia
	13743	R.	103.6	1,200	U-2; plain broth	
2	15223	R., Nog.	104.6	1,200	SA-2; tomato extract	Died; aplastic anemia
3	14168	R.	103.0	18,600	SG-3; plain bouillon	Died; acute myeloblastic leukemia
4	15554	R.	102.6	.....	SG-2, 5; dextrose and peptone flasks	Died; acute leukopenic myeloid leukemia
5	17950	R.	103.8	18,200	SA-2; dextrose and tomato extract	Died; pernicious anemia bronchopneumonia
6	14110	R.	105.0	.....	U-3; fluid mediums	Well; cervical adenitis (incision and drainage)
7	14801	R.	101.0	10,450	SG-2; enterococcus in dextrose and peptone flasks	Died; chronic ulcerative colitis
8	16089	R.	104.0	6,400	U-2; dextrose flask	Died; chronic ulcerative colitis; tonsillitis
9	17607	R.	101.8	13,300	S-4; dextrose and tomato extract	Died; chronic ulcerative colitis
	17612	R.	103.2	7,800	U-4; plain bouillon	
10	16822	R.	104.0	.....	SA-3; dextrose bouillon, and 1 colony on dextrose serum agar	Well; acute colitis complicating prostatectomy
11	14969	R.	100.6	.....	SA-1; all mediums; colonies too numerous to count	Died; meningitis; Streptococcus viridans; necropsy
12	15142	R., Ros., Liv.	.....	8,800	U-2; tomato extract	Died; meningitis tuberculous ?
13	15477	R.	104.2	11,400	SA-1; 60 colonies per cubic centimeter of blood	Well; meningococcus meningitis
		R.	.....	.....	0	
14	15649	R.	103.0	.....	SG-4; fluid mediums	Well; meningococcus meningitis
15	13447	R.	104.0	47,000	SG-1; 2 colonies per cubic centimeter of blood	Died; lung neoplasm; hemothorax
16	14010	R.	105.8	26,000	SA-2; all fluid mediums	Well; lobar pneumonia
		R.	.....	.....	0	
17	14206	R.	105.0	15,500	SG-4; plain and dextrose flasks; not bile-soluble; did not grow in mouse	Well; bronchopneumonia
18	14213	R.	103.6	25,800	SA-4; plain and dextrose flasks; not a pneumococcus	Well; bronchopneumonia
19	15612	R.	103.0	13,300	SA-4; 2 colonies per cubic centimeter of blood on 1 plate only	Well; lobar pneumonia
20	17469	R.	102.0	8,200	SA-1; tomato extract	Well; lobar pneumonia
21	17837	R.	103.0	25,000	SA-2; tomato extract	Well; pleuropneumonia
22	14843	R.	101.9	.....	U-2; dextrose and tomato extract	Well; grip
23	17850	R.	100.6	19,200	SA-4; dextrose broth only	Well; pyelitis
24	14683	R.	103.4	12,750	SA-4; peptone flash	Well; pyelitis
25	14718	R.	103.6	.....	SA-4; peptone and tomato extract	Well; pyelitis
26	16095	R.	100.0	.....	SA-4; 1 flask	Improved; pyelonephritis
27	14492	R., Liv., Ros., Nog.	102.6	.....	SA-2; plain broth flask	Improved; glomerulonephritis; benign hemorrhagica

* Explanation of abbreviations and numerals: R. indicates routine culture medium; Ce., Cecil technic; Ros., Rosenow's medium; Liv., cooked liver anaerobic medium; Nog., Smith-Noguchi medium; SA, Streptococcus alpha (viridans); SG, Streptococcus gamma (nonhemolytic); S, Staphylococcus albus; U, unidentified gram-positive cocci in short or long chains, which failed to grow in subculture. The numerals represent the day of subculture.

Cases of Nonrheumatic-Rheumatoid Disease with Nonhemolytic Streptococci or U Cocci in the Blood—Continued*

Case	Blood Culture No.	Mediums	Temperature, F.	White Blood Cells	Bacteriologic Findings	Clinical Result and Diagnosis
28	15022	R.	99.2	.....	SG-2; plain broth only	Well; pyelonephritis; adenoma of prostate (prostatectomy)
29	14907	R.	105.2	12,000	U-2; 1 flask	Improved; erysipelas of face; pansinusitis
30	17553	R.	105.0	20,000	SG-2; dextrose flask	Well; erysipelas; abscess of foot
31	18785	R.	102.6	21,250	SG-1; all mediums 2 colonies per cubic centimeter	Died; erysipelas of biopsy wound; lymphosarcoma
32	15068	R.	103.4	25,000	SA-4; fluid medium	Well; acute mastoiditis
33	14984	R., Ros., Liv.	101.4	20,000	SG-4; anaerobic medium only	Died; sinus thrombosis; acute mastoiditis
	15006	R., Ros., Liv.	.....	.....	SG-3; tomato extract aerobic	
34	14025	R.	103.8	.....	SA-2; tomato extract and dextrose serum medium; 2 colonies per cubic centimeter of blood	Died; sinus thrombosis; acute mastoiditis
35	14905	R.	102.0	16,000	U-4; tomato extract	Improved; abscess of thigh and penis
36	17856	R.	103.8	.....	SA-1; dextrose flask	Well; phlegmon of chest well; incision and drainage
37	13582	R.	104.0	.....	SA-2; dextrose flask	Well; abscess of thigh
38	18206	R.	102.8	4,800	SA-2; tomato extract	Died; parotid abscess
39	13635	R.	99.0	.....	SA-2; flasks	Died; parotid abscess
40	15245	R., Ros., Nog.	105.6	9,000	SA-4; aerobic	Died; postpartum sepsis
	15261	R., Liv.	104.8	.....	SA-2; aerobic and anaerobic fluid medium	
	15265	R., Liv., Ros.	105.5	14,000	SA-3; aerobic and anaerobic fluid medium	
41	13995	R.	105.0	.....	SG-2; dextrose broth; no plates made	Died; streptococcus sepsis
42	15027	R.	104.0	11,300	SA-2; all mediums	Died; streptococcus sepsis; peritonitis
43	17892	R.	101.0	8,600	Several greenish colonies on dextrose agar plates; failed to grow on transplant	Well; typhoid fever
44	13742	R.	101.6	10,600	U-2; flasks	Well; periostitis
45	17126	R., Liv.	99.0	.....	SA-4; anaerobic medium	Improved; osteomyelitis of clavicle and femur; incision and drainage
46	16653	R.	.....	.....	SG-2; flasks only; in transplant growing on anaerobic plates	Improved; sacroiliac arthritis
47	16722	R., Liv., Ros.	102.2	.....	SG-4; 1 flask	Died; carcinoma of ascending colon; fecal fistula
48	15122	R., Nog.	104.0	.....	SA-2; dextrose and tomato extract flasks	Died; stenosis of common bile duct; liver abscess
	15160	R., Liv., Nog.	103.8	17,600	SA-2; fluid aerobic and anaerobic medium	
49	17335	R.	101.8	.....	SA-4; dextrose flask	Improved; gonorrheal salpingitis; arthritis of right knee
	17360	R., Ce.	101.0	.....	SA-3; all routine flasks	
50	13877	R.	99.6	.....	SG-2	Well; erythema multiforme
51	14837	R., Ros., Liv., Nog.	.....	.....	SA-2; aerobic, dextrose flask	Well; right inguinal hernia; chronic appendicitis; herniaplasty

VIII. *Meningococcus Meningitis.*—There were 54 cases in this group, with 2 positive results (4 per cent) on routine mediums (see table, cases 13 and 14). In 1 case Streptococcus alpha was obtained (60 colonies per cubic centimeter); in another case, Streptococcus gamma. The patients in both cases recovered.

IX. *Pyelitis and Pyelonephritis.*—There were 72 cases in this group, with 5 positive results (7 per cent), as shown in the table (cases 23, 24, 25, 26 and 28). Routine mediums were employed in all cases. Streptococcus alpha was obtained 4 times; Streptococcus gamma, once. All of the patients recovered. In 1 case the urine was not cultured. In 1 case the culture of the urine was negative; in 3 cases, it contained B. coli.

COMMENT

Before proceeding with the comment, one must bear clearly in mind the fact that to all intents and purposes there exist 2 types of streptococcemia: One is associated with a massive blood invasion such, for example, as occurs in subacute bacterial endocarditis. In these cases numerous colonies are found in solid as well as in fluid mediums. On the other hand, in the individual diseases forming the 9 groups referred to, the streptococcemia is minimal and irregular. Very often repeated cultures fail to confirm the finding of organisms, and when they do grow they appear on solid mediums with extreme rarity. Libman [18] has called attention to this fact, and he has shown that this is a means of differentiating for practical purposes between the positive cultures obtained in cases of subacute bacterial endocarditis and those obtained in cases of rheumatic fever. For the sake of discussion, then, we may say that the 9 diseases considered in this article are associated with a "transitory bacteremia" or a "transitory streptococcemia."

In an attempt to arrive at the possible significance of these "transitory streptococcemias," especially those found in our control cases, several important points must be considered. These may be stated in the form of the following questions:

1. Are our control groups adequate?
2. Do these bacterial invasions occur shortly before death; i.e., are they agonal?
3. Was the patient's illness caused by the streptococcus recovered from the blood stream?
4. Were our methods of blood culture adequate?
5. What is the relative value of the culture methods used?

In order to answer the first question, it is advisable to compare our control group with the diseases making up the rheumatic-rheumatoid group. The group of 188 cases of acute rheumatic fever with polyarthritis had an 8 per cent incidence of nonhemolytic streptococcemia (4 cases Streptococcus alpha; 11 cases Streptococcus gamma); the

group of 126 cases of chronic rheumatic cardiovalvular disease had a 5 per cent incidence of nonhemolytic streptococcemia (3 cases Streptococcus alpha; 3 cases Streptococcus gamma), and the group of 48 cases of rheumatoid arthritis had a 4 per cent incidence of nonhemolytic streptococcemia (Streptococcus gamma). Taken together, these selected groups form a total of 363 cases with an incidence in nonhemolytic streptococcemia of 6 + per cent.

Compared to this our control groups are, on the whole, smaller (obviously due to the fact that these diseases were not especially studied for bacteremia), yet taken together they number 220 cases, in 8 of which Streptococcus alpha was recovered from the blood and in 6, Streptococcus gamma (the U cocci are not considered). This totals 14 cases with an incidence of nonhemolytic streptococcemia of 6 + per cent, which is the figure obtained for the rheumatic-rheumatoid group. Furthermore, with the exception of a single small group (aplastic anemia), the individual control groups show an incidence of nonhemolytic streptococcemia that runs fairly consistently around the 6 per cent mark. Since we are not interested in the individual control groups for the diseases per se, and, furthermore, since there are no very wide differences between them in the incidence of nonhemolytic streptococcemia, it seems to us to be permissible to add them together for control purposes. We therefore feel that our collective control material of 220 cases is adequate.

The mortality rates in the control groups (100, 100, 100, 100, 0 and 0 per cent, respectively) by their very nature must necessarily be high. This, however, by no means invalidates the findings, because in no instance was the blood culture taken less than ten days before death. Usually it was taken several weeks before death. Obviously, therefore, the patients were not moribund at the time. Then, too, more than half of the total control material (groups VIII and IX) was associated with no fatality, yet the incidence of nonhemolytic streptococcemia is about the same as in the rest of the groups.

In considering the possible relationship between the organisms found on blood culture and the diseases constituting the control groups, it is obvious that aplastic anemia, pernicious anemia, leukemia and meningococcus meningitis may be immediately dismissed from consideration on this account. Cultures of the urine in the cases of pyelitis and pyelonephritis did not implicate the nonhemolytic streptococci as responsible for the disease. There remains the colitis group, which must be considered mainly because of Bargen's [25] claims that a streptococcus is the etiologic agent in this disease. However, as will be noted, in the 2 posi-

25. Bargen, J. A.: Chronic Ulcerative Colitis, Arch. Int. Med. **45**:559 (April) 1930.

tive cases different organisms were obtained by us (Streptococcus alpha and Streptococcus gamma). Furthermore, Crohn and Shwartzman [26] reported on the same cases, and, while not denying the possibility that these organisms may play an etiologic rôle in the disease itself, gave ample reasons for believing that they are probably secondary invaders.

The adequacy of our methods was shown in several ways: First, positive cultures were obtained in a high percentage by our methods from cases obviously associated with streptococcemia. Thus, during the entire period of five years covered by this study, 23 cases of subacute streptococcus endocarditis in the active stages (i. e., bacteria in the vegetation crushings) came to autopsy, and in 21 of these (95.5 per cent) the organisms were easily cultivated from the blood. Furthermore, the average percentage of positive cultures in the cases in the hospital on the whole presents a remarkable constancy year in and out, showing that there is no appreciable variation in the sensitiveness of the mediums or any peaks of unusually high incidence in positive cultures.

Apart from this—and this brings us to the fifth question—our routine mediums acquitted themselves better than the special mediums employed. Thus, taking all the cases comprising the rheumatic-rheumatoid group, nonhemolytic streptococci grew 27 times in 347 cultures when routine mediums were employed (8 per cent), 6 times in 145 cultures by the special aerobic method (4 per cent), once in 127 cultures by anaerobic methods (—1 per cent) and not at all in the 16 Cecil cultures. As was pointed out, on a few occasions streptococci grew by the special aerobic method alone. For this reason, this method may be considered a useful addition to blood culture technic. In a very limited experience, the Cecil methods proved inferior to the routine method in our hands.

It is held by many that rheumatic fever and rheumatoid arthritis are associated with a consistent streptococcemia, that with special methods the incidence of positive blood cultures is quite high, and that while streptococci may occur as transient invaders in other diseases, such an occurrence is quite rare. The facts presented in the article, however, are at variance with these views.

SUMMARY

In summarizing the facts presented, we may say that of 5,233 consecutive blood cultures taken during five consecutive years under practically the same conditions, positive bacteriologic findings were obtained in 762 subjects. On analyzing chiefly the incidence of streptococcemia of the alpha and gamma types in 9 diseases other than those associated with a massive streptococcemia (e. g., subacute bacterial

26. Crohn, B. B., and Shwartzman, G.: J. Lab. & Clin. Med. **14**:722, 1929.

endocarditis), it is found that acute rheumatic fever with polyarthritis forms a group of 188 cases with a nonhemolytic streptococcemia of 8 per cent; chronic rheumatic cardiovalvular disease forms a group of 126 cases with a nonhemolytic streptococcemia of 5 per cent; rheumatoid arthritis forms a group of 48 cases with a nonhemolytic streptococcemia of 4 per cent; aplastic anemia forms a group of 13 cases with a nonhemolytic streptococcemia of 15.5 per cent; pernicious anemia forms a group of 11 cases with a nonhemolytic streptococcemia of 5 per cent; meningococcus meningitis forms a group of 54 cases with a nonhemolytic streptococcemia of 4 per cent, and pyelitis and pyelonephritis form a group of 72 cases with a nonhemolytic streptococcemia of 7 per cent.

The first 3 diseases mentioned (the rheumatic-rheumatoid group) form a group of 363 cases, with an incidence of nonhemolytic streptococcemia of 6 + per cent. The last 6 diseases mentioned (control) form a group of 220 cases, with an incidence of nonhemolytic streptococcemia of 6 + per cent.

These studies also show that the bacterial invasions are not agonal, and that they are not the primary cause of the diseases comprising the control group. Furthermore, it is to be noted that the methods employed were adequate, and that, in our hands, our routine methods were at least as sensitive as the special aerobic, Smith-Noguchi, Rosenow and Cecil methods. Our experience with the last named method, however, is limited.

CONCLUSIONS

Study of 5,233 consecutive blood cultures in a general hospital shows that with adequately sensitive methods an incidence of nonhemolytic streptococcemia (alpha and gamma types) between 4 and 15.5 per cent with an average of 6 + per cent occurs in at least 9 diseases, i. e., acute rheumatic fever with polyarthritis, chronic rheumatic cardiovalvular disease, rheumatoid arthritis, aplastic anemia, pernicious anemia, leukemia, colitis, meningococcus meningitis and pyelitis and pyelonephritis. On the basis of the incidence of the "transient" streptococcemia alone, these organisms cannot justifiably be considered as the causative agents of these diseases.

Book Reviews

Pediatric Education. Report of the Subcommittee on Medical Education, White House Conference on Child Health and Protection. Borden S. Veeder, Chairman. Section on Medical Service. Committee on Medical Care for Children. Paper. Pp. 109. New York: Century Company, 1931.

"All our knowledge of the preservation of the health of the child, the prevention of disease, and the care of the sick or abnormal child comes directly from the medical sciences. In organized health work which has so largely occupied the time of the White House Conference on Child Health and Protection we are apt to forget that the vast majority of American children today are dependent on the interest and care of a private physician for their physical well-being and health, and not upon an organization."

With these ideas in view, the subcommittee on medical education undertook a study of medical education so far as it related to the teaching of pediatrics in the medical schools, and to pediatric practice as current in the medical profession today. The committee sent questionnaires to pediatricians, physicians especially interested in pediatrics and general practitioners. There were 3,569 questionnaires sent, and 2,374, or 67 per cent, replies were received.

Of those practicing pediatrics wholly or mainly, 44 per cent felt that their course pertaining to the normal child and his health was mediocre or unsatisfactory in view of their present experience. "Further, the number who regarded the course as very satisfactory increases steadily the more recent the graduate." "Lack of clinical experience" is the most commonly mentioned deficiency. "Neglect of consideration of the normal child" is second, and "too little time given to pediatrics" is third.

More than two thirds of the men in general practice for ten or fifteen years feel that their course in pediatrics was satisfactory. Instruction as a whole in "contagious diseases" seems to have been most satisfactory, and that in "preventive measures" and "new-born" comes second. The most unsatisfactory course appears to have been that in "minor ailments."

Medical schools show the greatest variations in the size of the student body and faculty, yet all cover the same work in the same time. There is the greatest difference in arrangement of curriculums and methods of presentation. It was found that 35 per cent of the medical schools studied had insufficient hours to teach pediatrics properly, this deduction being made from the amount of time most schools find it necessary or desirable to assign to the subject. Only half of them use the well-baby clinic as a teaching facility. Over half of the schools reporting on their teaching on the newly born give less than ten hours' instruction. In quite a large number of the schools the facilities for bed-side teaching of communicable diseases in childhood are quite inadequate. As a whole, most of the medical schools today have adequate teaching facilities in the form of available hospital beds for the pediatric department, but in a few schools the teaching facilities are obviously inadequate.

Postgraduate work is being given by two methods: (1) intensive courses of review given in hospitals and medical centers during certain periods of the year; (2) extension courses given by visiting instructors in communities. Of physicians listed as specialists, 67 per cent had taken postgraduate instruction. Interest in postgraduate work was not confined to certain localities, but was well distributed over the country. The indication was that if proper courses were offered there would be no lack of physicians who would take advantage of them.

The conclusions that the subcommittee reached were: 1. Pediatrics should be recognized as a fundamental branch of clinical medicine and should be organized as an independent department of medical schools. 2. Adequate teaching staff,

hospital and clinical facilities and laboratories should be provided. 3. Special stress should be laid on the teaching of growth and development of normal children of all ages, individual and social preventive medicine, diseases of childhood and nutrition. 4. The minimum time devoted to pediatrics by the undergraduate student should be two hundred hours, with possible additional electives. 5. Correct pediatric pedagogy should be studied and intensive review and extension courses provided for postgraduate study.

The reading of the details of the report will be a great benefit to any one interested in the progress of pediatrics.

Imhotep to Harvey: Backgrounds of Medical History. By C. N. B. Camac. With a foreword by Henry Fairfield Osborn. Price, $3.75. Pp. 324. New York: Paul B. Hoeber, Inc., 1931.

Camac, in this book (Imhotep representing early Egypt, about 3000 B. C., and Harvey representing the seventeenth century), has presented a general survey of medical history covering a period of, roughly, four thousand, five hundred years. The rise of medical science is shown in relation to learning in general, other sciences and philosophy. One might say that intellectual development (used in the broad sense) throughout this time is the fabric of the book, while medicine appears as the most conspicuous thread. This thread sometimes becomes so thin as almost to disappear, but when this occurs the fabric itself appears defective and all learning is at low ebb. The most conspicuous flaw is, of course, the Middle Ages.

The construction of the book deserves comment. The author devotes a chapter (sometimes two) to each broad division in the history of science, e. g., pre-Greek science, Greek and Roman medicine, the Middle Ages—a period of the retrogression of science, the pre-Renaissance, the Renaissance and the seventeenth century. In addition, where it seemed necessary in order to effect a more thorough understanding, the author has inserted chapters dealing exclusively with the environment in which the scientist worked. There is also a chapter entitled "Schools of Thought in Medicine," and one containing historic records and quotations from various sources—some referring specifically to medicine, others not. He concludes the book with a bibliography of some length. One wishes that he might also have included an index. At the beginning of the chapters dealing with certain periods is a page or two containing information about those years in tabulated form. For example, in the chapter on Greek and Roman medicine the author includes in the summary pages a list of the pursuits of that time, the elements on which medical practices were based, the important records and the names and dates of the important writers and teachers. This device aided in unifying the period and helped to keep it clearly in mind. It was fitting to have the forward written by so fine a student of "origins" as Henry Fairfield Osborn.

The purpose of the book, as the author states at the outset, is to furnish a "background" of medical history; "he has drawn the picture in large strokes, leaving to the reader the filling in of detail which can be obtained from biographies and specialized works." The author goes far toward aiding the reader to fill in the details by his many references to representative and standard works. He hopes that by noting the reception accorded to the discoveries of the past, we may learn how to accept the achievements of our own time and avoid "disputes and dissensions, which discredit science." The environment in which the scientist labored throughout this long time is graphically depicted, so that one appreciates what was accomplished and understands why more could not have taken place.

This book should prove valuable and interesting to the medical profession: (1) to those especially interested in science who "may find here lessons applicable to our own times;" (2) to those engaged in teaching who will find descriptions of teaching institutions and methods; (3) to those who have a natural love of history and are desirous of learning all they can about the evolution of their profession; (4) to those who desire a handbook of medical history for reference to general

problems. The layman who has acquired an interest in medicine will find the book to his liking, as it is written in a manner that he can understand. In general, it is an excellent introduction to larger and more comprehensive books devoted to the history of medicine.

The book is written in a clear, interesting manner which is neither too detailed nor too abstract. The value of any such work lies in the author's ability to discriminate between the significant and the unimportant matters. The author of this book showed evidence of sound judgment in this respect. Furthermore, his study of various aspects of the periods he touches, say, the political, the religious and the cultural, has enabled him to draw a more complete and unified picture than he could otherwise have done.

Nucleic Acids. By P. A. Levene, The Rockefeller Institute for Medical Research, and Lawrence W. Bass, Assistant Director of Research, The Borden Company. American Chemical Society Monograph Series, no. 56. Cloth. Price, $4.50. Pp. 337. New York: The Chemical Catalog Company, Inc., 1931.

The subject matter in this monograph is presented in an entertaining, systematic and accurate style and from the historical point of view, because as the authors state in their preface, the progress in our knowledge on nucleic acids is largely through "paths of error and controversy" and "it would be an injustice to many if the monograph contained only the views that seem correct today." All the essential details on the chemistry of carbohydrates, imidazole, pyrimidine bases, purine bases and so on through the more complex units to the true nucleic acids are taken up in a uniformly systematic manner. Each chapter is devoted first to the organic chemistry of the group or individuals of the group; then follow the methods of preparation, specific properties, methods of separation and analytic and synthetic methods. The work of the master mind and hands is obvious throughout the monograph. The structural formulas are presented in a clear manner with Roman numerals for the text references. Naturally, the subject matter is brought up to very recent times, so that the new work on desoxyribosides, methylthiopentosides and the more complex polynucleotides is included. The authors appear to have some doubt as to the certainty of the separation of a 5-methylcytosine from tuberculinic acid. The physicochemical studies by Hammarsten and others on the polynucleotides are presented clearly. The book closes with a chapter on nucleases. Extensive author and subject indexes are included.

Der Mineralbestand des Körpers. By Wolfgang Heubner, Professor in Heidelberg. Paper. Price, 8.80 marks. Pp. 94, Berlin: Julius Springer, 1931.

This monograph was written in response to many requests for reprints of a similar compilation written by the author as part of a larger work some years ago. Résumés of this type have a definite value in spite of the unreliability of many of the values found in our periodicals. These are often unreliable because the methods are frequently at fault and also because considerable work is done by those who are not competent to make accurate analyses of this type. The author appears to realize these difficulties, although he does not seem to have attempted to select data with this criticism in mind. No attempt is made to discuss mineral metabolism, but only to present data on the amounts and state of various anions and cations in body fluids, cells and tissues. A brief discussion on the excess base values is included. Calcium and phosphorus naturally are discussed in considerable detail from the normal and pathologic point of view. Rarer inorganic constituents, such as fluorine, bromine, iodine, silicon, copper, manganese, aluminum and arsenic, are also taken up, especially in connection with their distribution in tissues. The author inclines to the view that most of these rarer constituents probably do not have a definite function in the living system, but that they occur there largely through accidental absorption from foods. The teeth, bones, muscle, heart, brain and skin are treated fairly completely.

Neue Wege der Blutdruckmessung. Fünfte Abhandlungen über Blutdruck und Puls in den grossen Arterien des Menschen. By Heinrich von Recklinghausen. Price, 12 marks. Pp. 289, with 82 illustrations. Berlin: Julius Springer, 1931.

Ostensibly written as an introduction to the use of the "grypotonograph," an apparatus for the oscillographic registration of blood pressure and pulse waves, this book turns out to be a thoroughgoing analysis of the theoretical concepts underlying the measurement of blood pressure, the comparison between direct and indirect methods, the "staircase curve" (pulse tracings obtained during inflation of the manometer cuff from levels below the diastolic to levels above the systolic arterial pressure) and many other interesting problems. Great emphasis is laid on the overpressure produced in the artery above the cuff as the result of artificial obstruction to the pulse wave in the compressed portion of the artery. The form of the individual pulse waves in the graphic record is made use of in determining systolic and diastolic pressures. Comparative data obtained through various methods of blood pressure estimation are critically discussed in the light of the physiology and pathology of the vascular system. Sources of error inherent in the recording apparatus itself are considered from a physical and a mathematical standpoint. Experts will probably not accept some parts of the general theory presented by the author, but serious consideration must be given to evidence submitted by one who has done fundamental research on blood pressure for more than a quarter of a century. This is not a book for the casual reader, though it is written clearly.

Varicose Veins: With Special Reference to the Injection Treatment. By H. O. McPheeters, M.D., F.A.C.S. Third edition. Cloth. Price, $4. Pp. 285, with 62 illustrations. Philadelphia: F. A. Davis Company, 1931.

The third edition of this monograph has been thoroughly revised and brought up to date by suitable additions. Most of the faulty references have been corrected although there are still a few misspelled names from the foreign literature. A new chapter has been added on the causes of failure in the injection treatment for varicose veins, containing a critical review of the published recurrences. The author does not condemn high saphenous ligation as strongly as in his previous writings, but still prefers injections into the proximal end of the saphenous trunk. As in previous editions, a whole chapter is devoted to prove the reverse flow of blood in varicose veins.

In the differential diagnostic table on vascular diseases, the data on arteriovenous aneurysms must be challenged. The figures on the oxygen content of venous blood are erroneous. The efficiency of drugs expressed in percentages seems somewhat artificial and arbitrary.

New refinements are added in the chapter on technic. On the whole, the present technic of the author seems unnecessarily complicated. Often heroic quantities of solution are introduced with as many as sixteen injections in one sitting. Such treatment can hardly be called a simple and painless procedure.

The printing and illustrations are excellent. To all who are interested in this field this challenging and stimulating contribution is strongly recommended.

Food Allergy: Its Manifestations, Diagnosis and Treatment, with a General Discussion of Bronchial Asthma. By Albert H. Rowe, M.S., M.D., Lecturer in Medicine in the University of California Medical School, San Francisco. Cloth. Price, $5. Pp. 442. Philadelphia: Lea & Febiger, 1931.

The author of this book has limited his discussion to the manifestations of allergy due to foods and has brought together and summarized the views of most of those who have written on the subject. The extensive bibliography is divided

into two parts, the first being the references related to food allergy, and the second being special references on other phases of allergy.

In his voluble enthusiasm on the subject the author explains, on the basis of allergy, many of the common constitutional disorders seen by internists, and he recommends his so-called "elimination diets" in their diagnosis and treatment.

The chapter on "elimination diets" includes many helpful recipes and suggestions. Careful and complete preliminary studies and later repeated observations of the patient are properly emphasized. Too frequent repetition of subject matter, too many case reports and the monotonous use of the expressions "in my experience," "in my opinion" and "my elimination diets" make it difficult to hold the reader's interest. Elimination of these faults would add to the enjoyment of the book. This book should be in the library of all students who are interested in dietary problems or who wish to obtain references to this type of literature.

Der Wasserversuch als Nierenfunktionsprüfung. Eine Zusammenfassung für den Kliniker und praktischen Arzt. By Dr. Med. Ferdinand Lebermann, Facharzt für innere Krankheiten in Würzburg. Price, 9.50 marks. Pp. 148, with 20 illustrations. Dresden: Theodore Steinkopff, 1932.

The author begins with a condensed but fairly complete review of the factors and problems underlying water balance. He then discusses the technic of the dilution and concentration test, the results in normal persons and in patients with the various forms of renal disease and the effects of using diuretics or pituitary extract during the test. There is adequate consideration of extrarenal factors and dilution of the blood as influencing the response to water given by mouth. One gets the impression that the interpretation of a diminished or a delayed excretion of water during the dilution test is so complicated in many instances as to render the procedure valueless. The simplicity of the method is evidently no guarantee for the reliability of the results. Perhaps the most valuable feature of the "Wasserversuch" is its ability to demonstrate latent cardiac edema. After reading through this monograph, one wonders at the remarkable European popularity of the dilution test for renal function. The bibliography will be useful to those who are specially interested.

Approved Laboratory Technic. By J. A. Kolmer and F. Boerner. Price, $7.50. Pp. 663, with 11 colored plates and 300 illustrations. New York: D. Appleton & Company, 1931.

This volume was prepared by the authors for the American Society of Clinical Pathologists. It includes instructions for the examinations of the blood, urine, gastric secretions, exudates and tissue fluids; helpful suggestions for the care and housing of the usual laboratory animals; recipes for mediums, stains and reagent solutions; procedures for bacteriologic technic and the identification of the common pathogenic bacteria and molds; methods for milk and water analyses; technic for the complement fixation and precipitation tests for syphilis; directions for quantitative analyses of the blood and urine; information needed in determining basal metabolism; instructions for preparing sections of tissues; and outlines for certain toxicologic examinations and tests for pregnancy. These directions are adequate, and the tests described include those generally demanded of a large hospital or commercial clinical laboratory. There are no instructions for postmortem technic and other procedures in the morgue. This is anomalous, since clinical pathologists are primarily pathologists in the original sense of the term.

A Diabetic's Own Cook Book. By Stella H. Lyons. Price, $2. Pp. 94. New York: Alfred A. Knopf, 1932.

The foreword of this book is written by Logan Clendening, M.D. He expresses his appreciation of the author as a cook and explains that the little book is in no

sense intended to supplant the physician's instructions to the patient. The diabetic patient will do well to bear this in mind as he reads, for the author says that her real mission is to remove food scales from the layman. Such teaching may be safe for the patient with mild diabetes "on the shady side of forty," as Dr. Clendening writes, but it may also be disastrous to the patient with severe diabetes, be he young or old.

Seventy of the ninety-four pages are filled with recipes and directions for the preparation of food. Ingredients for recipes are measured, but in the end the author ventures to give the food value of single portions of some recipes in fractions of grams of carbohydrate, protein and fat. Patients trained in food values and diet calculation will question the possibility of using "rye bread crumbs or washed bran" without considering the difference in carbohydrate content.

The suggestions offered for the preparation of food are extremely helpful to the patient who lacks imagination, but much of the teaching in unsound.

Manual for the Jewish Diabetic. By William S. Collens, B.S., M.D., Price $2. Pp. 138. New York: Bloch Publishing Company, 1931.

This is another little book on diabetes. It has as a special appeal a list of diets particularly designed for Jewish diabetic patients. Since the Jews seem to form an undue percentage of the diabetic patients of America, such a book should have a field of usefulness.

We are not convinced that "modern management, simple, easily executed, and rational, brings the diabetic condition rapidly under complete control and restores the person with diabetes to a state of good health." Certainly the text of this book is not as simple to understand as the author seems to consider the disease.

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